Technical Brief
Number 37

Prevention, Diagnosis, and Management of Opioids, Opioid Misuse, and Opioid Use Disorder in Older Adults

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new healthcare technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

This EPC evidence report is a Technical Brief. A Technical Brief is a rapid report, typically on an emerging medical technology, strategy or intervention. It provides an overview of key issues related to the intervention—for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Although Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions, the decision to request a Technical Brief is not solely based on the availability of clinical studies. The goals of the Technical Brief are to provide an early objective description of the state of the science, a potential framework for assessing the applications and implications of the intervention, a summary of ongoing research, and information on future research needs. In particular, through the Technical Brief, AHRQ hopes to gain insight on the appropriate conceptual framework and critical issues that will inform future research.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this Technical Brief, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions and the conceptual framework, the EPC consulted a panel of Key Informants who represent subject experts and end-users of research. Key Informant input can inform key issues related to the topic of the Technical Brief. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions, including the conceptual framework, do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Prevention, Diagnosis, and Management of Opioids, Opioid Misuse, and Opioid Use Disorder in Older Adults

Structured Abstract

Background. Opioid-related harms are increasing among older adults. Until we better understand the factors contributing to this trend, we will be unable to design and implement effective interventions to optimally manage opioid use and its potential harms among older adults. Although considerable research has been done in younger or mixed-age populations, the degree to which it is directly applicable to older adults is uncertain.

Objectives. To provide a framework for understanding how to reduce adverse outcomes of opioid use among older adults, and to describe the evidence available for different factors associated with and interventions to reduce adverse outcomes related to opioid use in this population.

Approach. With input from a diverse panel of content experts and other stakeholders, we developed a conceptual framework and evidence map to characterize empirical studies of factors associated with opioid-related outcomes and interventions to reduce opioid-related harms in older adults. We identified relevant literature among older adults (age ≥60 years) for an evidence map by systematically searching PubMed, PsycINFO, and CINAHL for studies published in English between 2000 and May 6, 2020.

Findings. We identified 5,933 citations, from which we identified 41 studies with multivariable models of factors associated with opioid-related outcomes and 16 studies of interventions in older adults. More than half (22/41) of the multivariable analysis studies evaluated factors associated with long-term opioid use (which, though not a harm per se, may increase the risk of harms if not appropriately managed). Prior or early postoperative opioid use, or greater amounts of prescribed opioids (high number of opioid prescriptions or higher opioid dose), were consistently (100% agreement) and strongly (measure of association ≥2.0) associated with long-term opioid use. Back pain, depression, concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), and fibromyalgia also had consistent, but weaker, associations with long-term opioid use. Several factors were mostly associated (>75% agreement) with long-term opioid use, including benzodiazepine use, comorbidity scores, (generally undefined) substance misuse, tobacco use, and low income. However, studies were mostly consistent that alcohol abuse and healthcare utilization were *not* associated with long-term opioid use. Gender, age among older adults, Black race, dementia, rural/nonurban residence, prescription of long-acting opioids, unmarried status, and use of muscle relaxants were variably associated (<75% agreement) with long-term opioid use.

Six studies examined factors associated with opioid-related disorders, although only one study evaluated factors associated with opioid use disorder. Alcohol misuse and gender were variably associated with opioid misuse (examined by three studies each).

All other evaluations of specific pairs of associated factors and outcomes of interest were evaluated by only one or two studies each. These included analyses of factors associated with multiple opioid prescribers, mental health outcomes, physical health outcomes, all-cause hospitalization, opioid-related hospitalization, nonopioid-specific hospitalization, emergency department visits, opioid overdose, all-cause death, opioid-related death, and nonopioid-related death.

The evidence on interventions directed at older adults is sparse. Of the 16 studies of opioid-related interventions in older adults, six examined screening tools to predict opioid-related harms, but none of these tools was tested in clinical practice to assess real-world results. Two studies found that prescription drug monitoring programs are associated with less opioid use in communities. Other studied interventions include multidisciplinary pain education for patients, an educational pamphlet for patients, implementation of an opioid safety initiative, provision of patient information and pain management training for clinicians, a bundle of educational modalities for clinicians, free prescription acetaminophen, a nationally mandated tamper-resistant opioid formulation, and motivational interview training for nursing students. Few intervention studies evaluated pain or other patient-centered outcomes such as disability and functioning.

Conclusions. The evidence base that is directly applicable to older adults who are prescribed opioids or have opioid-related disorders is limited. Fundamental research is necessary to determine which factors may predict clinically important, patient-centered, opioid-related outcomes. Studies to date have identified numerous possible factors associated with long-term opioid use (whether appropriate or not), but analyses of other opioid-related outcomes in older adults are relatively sparse. Research is also needed to identify interventions to reduce opioid prescribing where harms outweigh benefits (including screening tools), reduce opioid-related harms and disorders, and treat existing misuse or opioid use disorder among older adults.

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Evidence Summary

Main Points

We developed a Conceptual Framework outlining the stages of care for older adults who require or use opioids, and factors impacting management decisions and patient outcomes (see Figure A). The framework prioritizes three potential targets to determine factors associated with and interventions for: (1) reducing opioid prescriptions where harms outweigh benefits, (2) preventing opioid misuse and opioid use disorder (OUD), and (3) reducing other opioid-related harms.

- The current literature on risk factors is mostly sparse, particularly for the most relevant patient-centered outcomes. The studies were not designed to evaluate predictive models or screening tools for clinical decision making. We found 41 studies that used multivariable analyses assessing factors independently associated with opioid-related outcomes among older adults (≥60 years).
    - 22 multivariable studies evaluated **long-term opioid use**, which is not specifically a high-risk behavior and may indicate continuing pain symptoms, but does increase exposure and, therefore, potential for opioid-related harms.
        - All 9 studies that looked at prior or early postoperative opioid use found mostly strong associations (e.g., relative risk [RR] >2.0) with long-term opioid use.
        - All 9 studies that examined greater amounts of prescribed opioids (higher number of opioid prescriptions or higher opioid dose) found mostly strong associations with long-term opioid use.
        - Other factors with consistent (100% agreement), but largely weak associations (e.g., RR <2.0, but statistically significant), included back pain, depression, concomitant NSAID use, and fibromyalgia.
        - Studies were mostly consistent (≥75% agreement) that concomitant benzodiazepine use, higher comorbidity score, (generally undefined) substance misuse, tobacco use, and having a low income were each associated with long-term opioid use, but the associations were mostly weak.
        - In contrast, studies were mostly consistent that alcohol "abuse" and healthcare utilization were *not* associated with long-term opioid use.
    - Across 6 studies evaluating opioid-related disorders, including OUD and opioid misuse, 3 studies each had variable findings regarding the associations of alcohol misuse and of gender with **opioid misuse**.
    - All other evaluations of specific factors and outcomes of interest were evaluated by only one or two studies each. These included factors associated with **opioid use disorder**, **high-risk obtainment of prescription opioids**, **procuring multiple opioid prescribers**, **mental health outcomes**, **physical health outcomes**, **all-cause hospitalization**, **opioid-related hospitalization**, **nonopioid-specific hospitalization**, **emergency department visits**, **opioid overdose**, **all-cause death**, **opioid-related death**, and **nonopioid-related death**.
- The literature on interventions specifically intended for or evaluated in older adults is sparse. 16 studies addressed interventions related to opioid use and opioid-related

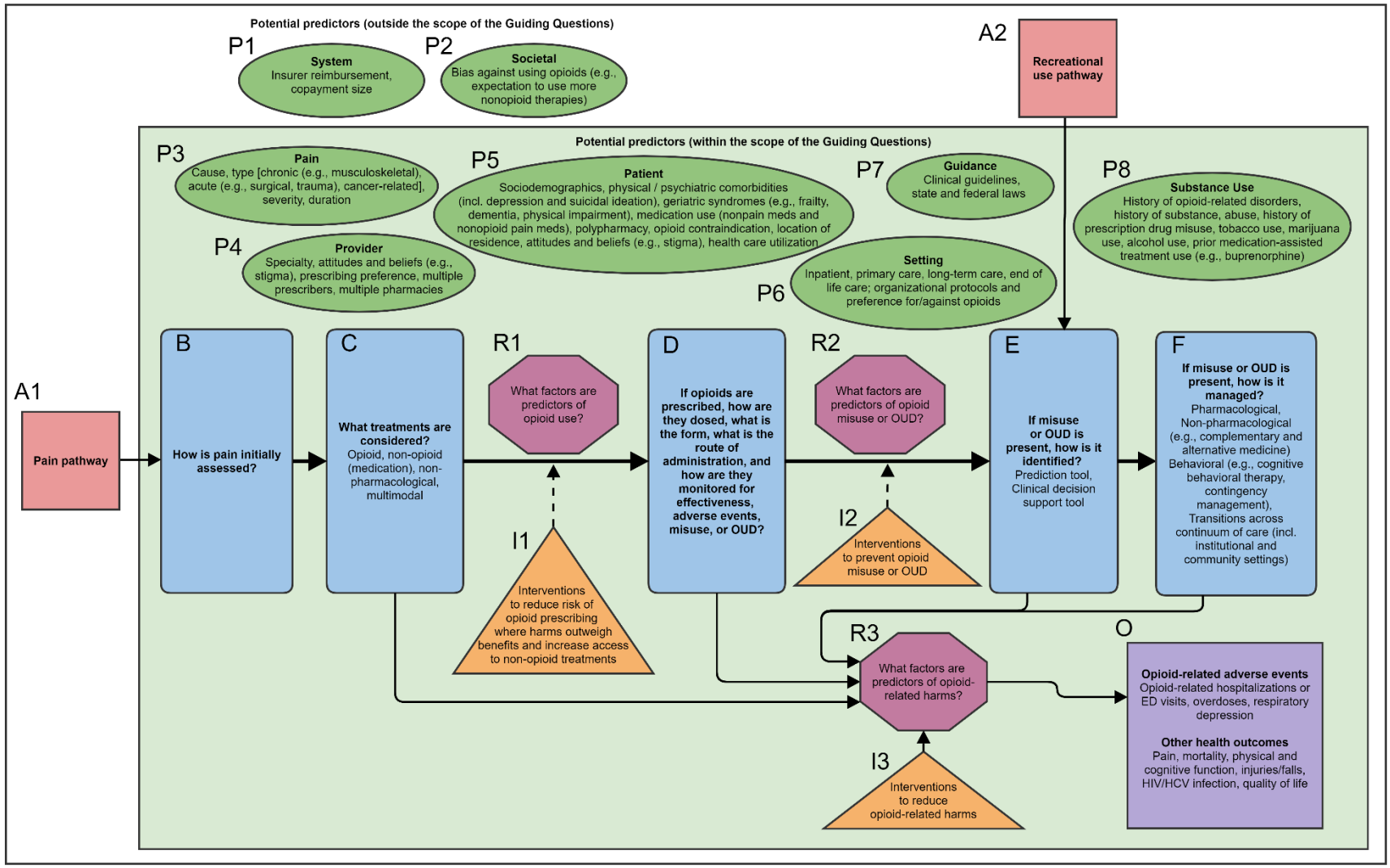
disorders in older adults. Only 2 studies were randomized controlled trials. Each intervention was evaluated by one, or in two instances, two studies.
    - The most-studied interventions were **screening tools to predict opioid-related harms,** but none of these tools has been tested in large, national populations of older adults to assess real-world results or clinical outcomes related to their use.
    - 2 studies found that **prescription drug monitoring programs** have been associated with less opioid use (at the State level) but did not address appropriate use.
    - Other studied interventions include included **multidisciplinary pain education for patients**, an **educational pamphlet for patients**, **implementation of an opioid safety initiative**, **provision of patient information and pain management training for clinicians**, a **bundle of educational modalities for clinicians**, **clinician education**, **free prescription acetaminophen**, a nationally-mandated **tamper-resistant opioid formulation**, and **motivational interview training for nursing students**.
    - Among studies that had the **goal of reducing overall opioid prescriptions or use**, none specifically assessed "appropriate" reduction of opioid prescriptions or use (e.g., when the risks of opioid use outweigh the benefits). Few evaluated patient-centered outcomes, including pain and functioning.
- Future research is needed of studies in older adults to establish factors associated with clinically-important, patient-centered opioid-related outcomes in older adults and to identify interventions to improve primary prevention (reducing unnecessary opioid use), secondary prevention (reducing opioid-related harms), and treatment of existing opioid misuse or OUD.

Background and Purpose

Opioid-related hospitalizations, emergency department (ED) visits, and deaths are increasing among older adults, even as rates of nonopioid-related hospitalizations and ED visits are decreasing. Older adults make up a growing share of the U.S. population and are at a greater risk of opioid exposure due to higher incidences of pain and comorbidities that result in pain. Older adults are also more likely than younger adults to experience adverse drug reactions and opioid misuse (related to both prescription and nonprescription opioids) is an increasing source of opioid-related harms among older adults. To address these issues, we need to examine the evidence base of studies of older adults to better understand the factors driving opioid-related harms in older adults and the evidence-based interventions to reduce those harms.

This Technical Brief provides a conceptual framework that diagrams the process of care to identify areas of risk and opportunities for intervention and describes the relevant evidence base. The framework and evidence map will support the Agency for Healthcare Research and Quality's (AHRQ) and other agencies' development of an evidence-based research agenda to answer the most important questions regarding prevention, diagnosis, health outcomes, and management of opioid use, misuse, and opioid-related disorders among older adults.

Figure A. Conceptual framework



See legend in full report.

Methods

We developed a Conceptual Framework based on existing frameworks and discussion with 15 Federal and non-Federal stakeholders (see Figure A). The Conceptual Framework identifies Guiding Questions regarding factors potentially associated with opioid-related outcomes (featured in the octagons) and relevant interventions (featured in the triangles). Using the Conceptual Framework as a guide, we conducted a literature search of relevant studies published between January 2000 and May 6, 2020. The review was conducted in accordance with the AHRQ EPC Program Methods Guidance for Technical Briefs.

Results

The Conceptual Framework outlines the stages of care for older adults related to opioid use as well as the factors that impact management decisions and patient outcomes. These include assessment of pain, selection of pain treatment, choice of opioid regimen, assessment for opioid misuse or opioid use disorder (OUD), and management of misuse or OUD (featured in Rectangles B to F). Multiple potential patient, provider, health system, and societal factors (in the 8 ovals) may influence risks of adverse outcomes and the effect of interventions to reduce the adverse outcomes (Box O). The framework includes factors associated with interventions to (1) reduce opioid prescriptions where harms outweigh benefits, (2) prevent opioid misuse and OUD, and (3) reduce other opioid-related harms.

Regarding factors related to opioid use and harms in older adults (≥60 years), we focused on the 41 studies that reported multivariable analyses to identify independent factors associated with the outcomes of interest. There were 22 studies that addressed long-term opioid use (categorized into Octagon R1 in the Conceptual Framework). Long-term opioid use is not specifically a high-risk behavior, and may indicate continuing pain symptoms, but it does increase exposure and, therefore, can be a useful outcome to aid with opioid management. Eight studies that addressed opioid misuse or OUD (related to Octagon R2) examined two sets of outcomes: opioid misuse (6 studies) and having multiple opioid prescribers (2 studies). While having multiple opioid prescribers is not an indication of opioid misuse, it may reflect a high-risk patient behavior and/or a lack of coordinated care. The 14 studies that addressed opioid-related harms (Octagon R3) had four sets of outcomes: mental or physical harms (4 studies), hospitalizations or ED visits (5 studies), opioid overdose (3 studies), and death (5 studies). Note that while we used standardized terminology to categorize factors and outcomes, to avoid distorting interpretation of each study's results we maintained their original terminology, even if currently out of date.

Among 22 studies evaluating **long-term opioid use** among older adults, 9 that examined opioid use prior to surgery or injury (or early use after surgery) and 9 that examined greater amount of opioid use (more prescriptions or higher dose) were consistent (in full agreement) that these factors are associated with long-term opioid use, with mostly strong associations (e.g., RR ≥2.0). Other consistent associations, but with largely weak associations (RR <2.0, but statistically significant), were found with back pain (7 studies, 3 with strong associations), depression (11 studies, all weak associations), concomitant NSAID use (4 studies, all weak associations), and fibromyalgia (3 studies, all weak associations).

Studies were mostly consistent (≥75% agreement) that benzodiazepine use (6 of 7 studies), higher comorbidity score (6 of 8 studies), variably or undefined substance misuse (9 of 10 studies), tobacco use (5 of 6 studies), and low income (8 of 10 studies) were associated with

long-term opioid use, but these associations were mostly weak. Studies were also mostly consistent that alcohol "abuse" (4 of 5 studies) and healthcare utilization (3 of 4 studies) were *not* associated with long-term opioid use. Numerous factors had variable findings (<75% agreement) of association or were evaluated by only one or two studies.

Only 16 studies addressed **interventions** to reduce opioid prescriptions, reduce opioid-related harms, or identify or treat opioid-related disorders; only two were randomized controlled trials. Nine studies evaluated a variety of different interventions to **reduce opioid prescribing or use** (depicted in Triangle I1); although none specifically focused on or attempted to account for whether harms outweighed benefits. Eight studies evaluated interventions to **identify or reduce opioid-related disorders** (Triangle I2); six of these studies evaluated five screening tools to identify people at increased risk of opioid-related disorders; two of the studies evaluated interventions to reduce opioid misuse. Two studies addressed interventions to **reduce opioid-related harms** in older adults (Triangle I3), one of which addressed management of a hypothetical patient with opioid misuse (Rectangle F). No study specifically addressed safe prescription practices to reduce harms among older adults appropriately using opioids (Rectangle D) or treatments of OUD.

The studies provide some preliminary evidence that various screening tools and interventions may be effective to reduce opioid use, reduce the risk of opioid misuse, and manage opioid misuse among older adults, but replication in well-designed studies is needed. Two studies found that prescription drug monitoring programs were associated with less opioid use (at the State level) but did not evaluate whether the change in opioid use was beneficial to patients. Overall, there has been little replication of evaluations of interventions and none of the screening tools have been tested in large, broadly representative populations of older adults to assess their real-world effects. No studies evaluated the management of actual (as opposed to hypothetical) older adults with opioid misuse or OUD (Rectangle F).

Limitations

Due to resource constraints, our literature search did not include studies published prior to 2000 and did not include all potentially relevant literature databases. In keeping with the intent of a Technical Brief (which is to provide a high-level overview of the evidence base and identify gaps) we did not fully assess the quality of each eligible study or the strength of evidence for any of the Guiding Questions.

Conclusions

The evidence base that is directly applicable to older adults who are prescribed or use opioids or who have opioid-related disorders is relatively sparse. Fundamental research is necessary to determine which factors may predict opioid-related harms for older adults. Current studies largely focus on amounts or duration of opioid use among older adults, without assessment of whether the opioids are necessary to control pain or the effect of interventions on patient-centered outcomes. Research is needed to identify interventions to reduce opioid prescribing where harms outweigh benefits, reduce opioid-related harms and disorders, and treat existing misuse or OUD among older adults. Future research should emphasize the adaptation of existing interventions for the general population specifically for use in older adults and should account for the heterogeneity of the older adult population. However, the development, validation, and evaluation of new interventions tailored to the needs of older adults will likely also be necessary to prevent and manage opioid misuse and OUD in older adults.

Introduction

Background

Between 2010 and 2015, opioid-related hospitalizations among adults aged 65 years and older increased by 34 percent, from 199.3 to 267.6 per 100,000 individuals, while nonopioid-related hospitalizations decreased by 17 percent.[1] Over that same period, opioid related emergency department (ED) visits among older adults increased by 74 percent.[1] Although younger age cohorts suffered larger absolute increases in opioid-related mortality between 2001 and 2016, opioid-related mortality also increased among adults between the ages of 55 to 64 and those that are 65 and older.[2] In addition, nonmedical prescription opioid use among individuals aged 65 years and older has doubled, from 0.4 percent in 2002 to 0.8 percent in 2014.[3] These data raise concerns regarding the current approaches to pain management with opioids, and prevention, diagnosis, and management of opioid misuse and opioid use disorder (OUD) among older adults.

Older Adults Are a Growing Population

The U.S. and global population of older adults is increasing, further creating a critical need to understand opioid use among older adults. The U.S. population aged 65 years and older is forecast to increase from 48 million people in 2015 to 88 million people in 2050.[4] The combination of the growing population of older Americans and the increasing rates of opioid-related harms in this population will likely result in even larger increases in the absolute numbers of opioid-related hospitalizations, ED visits, and mortality among older adults.

Pain in Older Adults

Older adults are more likely than younger adults to be exposed to opioids due to their high incidence of pain and need for acute and chronic pain treatment for conditions such as diabetic neuropathy, large joint osteoarthritis, fractures, and cancer. In older adults, compared with younger individuals, episodes of acute pain are more likely to transition to chronic pain due to biological changes in the nervous system, contributing to their experiencing severe or persistent pain.[5-7] Older adults may also have accumulated psychological (or emotional) trauma, resulting in anxiety and depression; loss of loved ones or other important individuals; an erosion of social roles; and occurrence of disability, all of which may increase the probability that an older adult uses opioids as a treatment for emotional and physical pain.[3] For these reasons, and more, pain management in older adults is particularly challenging.

Needs and Challenges of Pain Treatment in Older Adults

Optimizing the balance of benefits and risks for different pain treatments is particularly important for older adults. Opioid medications[a] are commonly used to treat pain; however their use, especially at higher doses, is associated with risk of opioid-related harms, including overdose.[8-12] Furthermore, data on the effectiveness of long-term opioid therapy are still unavailable for many sets of clinical circumstances.[13-15] Prior published evidence and guidelines focused on the general population have suggested that restricting opioids to severe pain or pain

[a] See *Definition of Terms* section at the end of the Introduction.

that has not responded to nonopioid therapy, using the lowest effective dose of short-acting opioids for the shortest duration possible, and co-prescribing opioids with nonopioid analgesics, but not other interacting medications, is the optimal approach.[16-19] At the same time, for many older adults, opioid use is an appropriate (or the only) option and may offer important benefits, such as improved quality of life and the ability to successfully conduct activities of daily living. For example, many older adults are unable to tolerate nonopioid analgesics (e.g., nonsteroidal anti-inflammatory drugs) due to impaired liver or kidney function, hypertension,[20-22] other cardiac risks,[23-29] concomitant anticoagulant therapy in atrial fibrillation or after stroke, risk of gastrointestinal bleeding,[30-33] or other conditions.[34] Since untreated pain has been associated with many negative consequences, including depression, anxiety, functional impairment, slow rehabilitation, decreased socialization, sleep and appetite disturbances, and greater healthcare utilization, the benefits of opioids may outweigh the risks.[35] Appropriate use of opioids under clinicians' supervision may provide many older adults with necessary pain relief, allowing them to remain active, independent, engaged in necessary therapy (e.g., rehabilitation or physiotherapy), and able to maintain a higher quality of life. In turn, opioids may help prevent or delay disability for years among many older adults. However, clinicians and other healthcare professionals need evidence-based information, education, and training to balance the benefits and risks of opioid use in their older patients.

Older Adults Are at Higher Risk of Adverse Events Even With Appropriate Opioid Use

Empirically, older adults are significantly more likely to experience adverse drug reactions than younger adults,[36, 37] and are at increased risk of opioid-related falls and fractures,[38-41] hospitalizations, ED visits, and death,[42] even when using opioids as directed and intended by the prescriber. The frequency of opioid-related hospitalizations and ED visits appears to vary geographically, presumably because of geographic differences in patients' characteristics and access to healthcare and other services and structures.[1]

Age-related physiological changes (e.g. in metabolism and body composition), drug-condition interactions, and polypharmacy (resulting in drug-drug interactions) all increase older adults' risk of opioid adverse effects, even when opioids are used as intended. Polypharmacy is highly prevalent in older adults and increases the risk of adverse drug-drug interactions. For example, combining opioids and benzodiazepines can result in respiratory depression and death.

Opioids may exacerbate pre-existing conditions such as cognitive impairment, compromised respiration, hypogonadism, osteoporosis, frailty (or diminished physical reserve), and other substance (e.g., alcohol) use disorders.[43-46] Reciprocally, unrecognized cognitive decline or dementia may lead to unintentional deviations from a prescribed opioid regimen, and accidental poisoning or overdose. These risks may be exacerbated by the high frequency at which older adults see multiple providers and specialists, who often do not coordinate their care and prescribe interacting or duplicative medications.[47,48]

Misuse of Opioids May Also Be Responsible for Opioid Adverse Events in Older Adults

It is unclear to what extent medical opioid use (as prescribed) versus nonmedical opioid use or misuse accounts for the increases in opioid-related harms over the past decade among older adults. Media coverage and research has focused almost entirely on opioid misuse among

younger individuals due to their higher prevalence of misuse.[1,2,49] Older adults might misuse prescribed opioids by taking them in greater amounts, more often, or for longer than they were directed to by a prescriber, or even resort to illicit opioids to alleviate untreated or undertreated pain, increasing the risk of overdose.[50] Opioid misuse, which may be in part due to inadequate pain management by clinicians, raises important questions about how to ensure that prescribers deliver adequate pain treatment to their older adult patients and thus avoid adverse events resulting from suboptimal treatment. Additionally, some older adults may attempt suicide via self-poisoning; suicide mortality appears to be increasing among older adults[51] and social isolation, depression, chronic pain, disability, and loss of functioning are all factors associated with suicide that are prevalent among older adults.[51]

As with younger individuals, opioid misuse may transition to OUD. Regardless of age, individuals may become physically dependent on opioids (i.e., the body adjusts its normal functioning around regular opioid use) and continue taking them to avoid uncomfortable withdrawal symptoms.[52,53] Physical dependence on opioids may be a precursor to, but does not indicate, opioid misuse or OUD. Older adults may also develop psychological and other types of dependence on opioids. Long-term opioid use—use of opioids on most days for longer than 3 months—may predispose individuals to developing OUD; although this connection has not been established in studies of younger or older adults. Some clinician-researchers have postulated that the identification of substance misuse problems in later life, such as opioid misuse or OUD, may be complicated by a clinical presentation that is similar to depression, delirium, or dementia in older adults.[54-56] The similarities between the symptoms of OUD and other geriatric syndromes may hinder identification of OUD among older adults.

Considering all of the aforementioned information, a better understanding of the current approaches to prevention, diagnosis, and management of opioids, opioid misuse, and OUD among older adults and the supporting evidence is necessary.

Overview of the Technical Brief

This Technical Brief comprises a conceptual framework and a focused evidence map of the current evidence base with the goal of understanding the issues that are driving the current rise in opioid-related morbidity, mortality, and other adverse events in older adults, and what evidence is needed to support effective interventions to prevent and manage harms from opioids in this population. The framework and evidence map will support the Agency for Healthcare Research and Quality (AHRQ) and other agencies to design an evidence-based research agenda to answer the most important questions regarding prevention, diagnosis, and management of opioid use, misuse, and OUD among older adults. The ultimate goals are to accelerate practice change and improve outcomes in older adults. This brief focuses on care management rather than societal or high-level system issues that are outside provider or health-system control.[57]

Definition of Terms

Opioid medications: All natural, synthetic, and semisynthetic substances that have effects similar to morphine, specifically those approved by the U.S. Food and Drug Administration (FDA) as medications (e.g., oxycodone).

Medical opioid use: Use of an opioid for a condition or a disease (an indication) for which reasonable scientific evidence supports that an opioid is an effective treatment.

Recreational opioid use: Use of an opioid for its psychoactive effects in the absence of a condition or a disease (an indication) that reasonable scientific evidence supports that an opioid is an effective treatment.

Multimodal Stepped Pain Therapy: A pain treatment approach that sequentially (1) combines medications from different pharmacologic classes and/or (2) combines pharmacologic and nonpharmacologic therapies or multiple nonpharmacologic therapies.

Prescribers: Healthcare professionals from any discipline who have the legal authority to prescribe opioids and other medications.

Long-term opioid use: Opioid use on most days for more than 3 months. Long-term use is defined regardless of the clinical appropriateness of the duration of opioid use.[15]

Opioid-related disorders: For the purpose of this report, any problematic opioid use, including OUD and opioid misuse, defined next.

Opioid use disorder (OUD): The diagnosis of problematic use of opioids as, for example, defined by DSM-V (Diagnostic and Statistical Manual of Mental Disorders) criteria.[58] OUD is the clinical term for opioid addiction. OUD is typically characterized by loss of control of opioid use, risky opioid use, impaired social functioning, tolerance, and withdrawal. Tolerance and withdrawal do not contribute toward a diagnosis of OUD when individuals are using opioids appropriately and under medical supervision. Diagnosis of OUD is made when a person uses opioids and experiences 2 or more of 11 symptoms in a 12-month period.

Opioid misuse: A problematic pattern of opioid use, distinct from OUD. Opioid misuse is not a clinical diagnosis. It is the use of opioids in any way (other than OUD) that is different than as directed by a prescriber (e.g., at higher doses, more frequently, or for longer duration than prescribed; for a reason other than indicated; without one's own prescription) or the use of any opioid in a manner, situation, amount, or frequency that can cause harm to self or others.[59]

Methods

We address three overarching research questions ("Guiding Questions") related to opioids in older adults:

1. What are the most important factors driving the increase in opioid-related hospitalizations and ED visits for older adults and what interventions are needed to reduce the risk of opioid-related adverse events, opioid misuse, and OUD in older adults without compromising pain control or quality of life?
2. Among older patients taking opioids, what factors are most strongly associated with harms from opioids (adverse events, misuse, or opioid use disorder)?
3. What interventions have been studied to help providers to
    a. reduce opioid prescription where harms outweigh benefits in older adults without compromising pain control or quality of life (e.g., shared decision-making)?
    b. reduce the risk of adverse events, misuse or opioid use disorder in older adults for whom opioids are appropriate?
    c. identify and treat opioid misuse or opioid use disorder in older adults?

In addition, we address the question of what research is necessary to develop interventions that improve the management of opioids and reduce the risk of opioid-related harms in older adults. The original Guiding Questions, which were more detailed, were developed by AHRQ in consultation with other federal agencies. The original questions can be found in Appendix B together with further details about the methods.

To address the issues raised by the Guiding Questions, we developed a conceptual framework informed by stakeholder (Key Informant) discussions and generated an evidence map of the existing evidence base. The conceptual framework and evidence map summarize the evidence in a way that allows stakeholders to readily identify the next steps for research on opioid use and misuse in older adults. Here we give an overview of the methods; details can be found in the Appendices.

Development of Conceptual Framework

Initial Development

A draft conceptual framework was developed to address Guiding Question 1 based on existing prior conceptual frameworks and systems maps, including those developed by Wakeland and colleagues,[60,61] the U.S. Department of Health and Human Services Pain Management Best Practices Inter-Agency Task Force Report,[62] and the National Academies of Sciences Engineering and Medicine report "Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use".[63] Existing frameworks and systems maps from other conditions not directly related to pain were considered to help inform alternative structures and formats for the framework.[64,65]

Key Informants and Discussions

We formed a 15-member panel comprising six individuals employed by Federal agencies and nine individuals employed by nonfederal entities. These individuals included experts in the care of older adults, experts in pain treatment and opioid use, nationally and internationally

recognized researchers, policy makers, and internationally recognized advocates for older adults with pain. The expertise of the Key Informants included geriatrics, pain medicine, addiction medicine, psychiatry, nursing, psychology, pharmacy, emergency medicine, and health policy. We had discussions with the 15 Key Informants to help us revise the conceptual framework. We solicited the panel's input in three teleconferences and over email until we deemed that we had sufficiently discussed all of the most relevant themes. The interactions with the Key Informant Panel were facilitated by the EPC and included several structured prompts based on all Guiding Questions. The Key informants were asked about the draft Conceptual Framework and to identify peer-reviewed publications or other relevant literature related to the topics of interest. In Appendix C we provide an overview of our discussions with Key Informants that helped to shape the Conceptual Framework and to evaluate the evidence base. Appendix C also includes specific themes identified during the discussions.

Evidence Map

We conducted a literature search to find articles primarily addressing Guiding Question 2 (factors associated with harms from opioids in older adults) and Guiding Question 3 (interventions that either appropriately reduce opioid prescribing and risk of harms, or identify and treat misuse and OUD in older adults). We primarily sought studies that pertain to the likelihood of opioid use, preventing opioid misuse and OUD and reducing opioid-related harms (relating to the three Octagons and Triangles in the Conceptual Framework (Figure 1).

The evidence map enumerates and describes the primary studies that directly address relevant questions pertaining to the management of opioid use and misuse in older adults. It forms a citation list and database for any future systematic review on the topic. In keeping with the intent of a Technical Brief, we did not assess their methodological quality. The literature search is described in Appendix A. Appendix B describes processes for abstract screening and further details about our methods to create an evidence map from full-text articles.

Based on discussions with the Key Informants and the variable definitions of "older adults" across studies, we focused on studies that included adults aged 60 and over. There is no standard definition of "older adult." Most studies, especially those based in the United States, used a threshold of 65 years, in keeping with Medicare eligibility criteria. To be more inclusive, we selected a threshold of 60 for our eligibility criteria; although, we recognize that some researchers consider adults 55 years, or even 50 years, to be potential thresholds to describe older adults in the context of opioid use. We restricted to studies conducted in high-income countries and excluded studies of older adults who were terminally ill, in hospice, or in similar situations where opioid harms, misuse, or OUD are of lesser concern. All factors associated with opioid misuse, harm, or OUD were considered and included, as were all factors and interventions regarding opioid use (including long-term opioid use), manage opioid use, or prevent opioid-related harms, including misuse and OUD. Any outcome (person-, provider-, and system-level) was eligible for inclusion. All primary study designs, as well as systematic reviews and clinical practice guidelines, were eligible for inclusion.

We searched PubMed, PsycINFO, and CINAHL, using terms related to older age or aging, crossed with terms for opioid use, opioid-related disorders, opioid misuse, and opioid-related adverse events. We did not include search terms for (and thus avoided excluding articles based on) interventions, outcomes, or study designs. We limited results to studies published in English, between January 1, 2000 and May 6, 2020. We restricted the time frame due to resource limitations (and, thus, feasibility). We chose a timespan of the past 20 years (specifically, since

1/1/2000), because older empirical data are less likely to be relevant to today's setting. Demographic and clinical characteristics of older adults have shifted dramatically over the last 20 years, so earlier evidence may not generalize well to a modern older adult population. Where earlier studies may also be applicable, important questions are often addressed by more recent replication studies, in which case they would be represented in the evidence map (with the possible exception of studies of pharmacological interventions, such as for treatment of OUD, that have not recently been investigated in older adults). Furthermore, the more recent literature is probably more relevant for informing the future research agenda.

To screen the evidence base, we used the online software Abstrackr, which uses machine learning algorithms to predict and sort citations based on likely relevance; using these algorithms, we stopped screening when the remaining prediction values suggested no further relevant citations would be identified.

We also searched ClinicalTrials.gov and PROSPERO to identify unpublished studies, ongoing studies, and unpublished systematic reviews. All potentially eligible citations were retrieved and screened in full text for eligibility by a single reviewer, after a training period to ensure consistency between all reviewers. Each eligible study was extracted for a limited set of elements on the population, the association variables (factors) or intervention, intent of interventions, examined outcomes, and study design features. All data were extracted into a predefined electronic form. Of note, we used standard terminology to categorize factors and outcomes, but we maintained the original wording used by the studies (e.g., "abuse") during extraction and study-level summarization to avoid misrepresenting the original studies, even if the language used by the studies' authors might currently be considered inappropriate or stigmatizing.

We provide a high-level summary of the body of evidence that evaluated putative factors that predict adverse outcomes related to opioids in older adults. The summary focuses on only multivariable analyses within clearly specified cohorts of older adults since these studies are more likely to reliably identify independent variables (factors) than studies performing univariable analyses of a single variable in each model. We then organized the data from the studies by factor and opioid related outcome. The measure of association estimates from these multivariable analyses were each categorized according to the direction of the association and by following schema:

- **Strong association**: a statistically significant association between a (categorical) factor and higher (or lower) risk of the outcome with a measure of association ≥2.0 (or ≤0.5); e.g., relative risk (RR) or odds ratio (OR).
- **Weak association**: a statistically significant association between a (categorical) factor and higher (or lower) risk of the outcome with a measure of association between 0.5 and 2.0
- **Statistically significant association**: for evaluations of continuous factors (e.g., age, per year) for which we could not estimate a standardized measure of association where the association was statistically significant (we did not classify these associations as strong or weak)
- **No statistically significant association**: for factors without a statistically significant association, regardless of magnitude of measure of association

In partial determination of the strength of the body of evidence, we assessed whether findings were consistent across studies. We found no guidance on how to assess consistency of

semiquantitative summaries of association studies. AHRQ guidance for assessing consistency across (primarily intervention) studies suggest consideration of direction and/or magnitude of effect (depending on the research question) and promotes the judgment of the researchers to determine consistency.[66] For the purpose of the qualitative assessment of the evidence base for this report, we established the following arbitrary criteria for different levels of consistency:

- A minimum of 3 studies had to evaluate the same factor category (e.g., age) for the same outcome (e.g., long-term opioid use). Associations with only one or two studies were not evaluated for consistency.
- "Consistent" – All studies agreed in both direction and statistical significance of association (e.g., all found significant associations between history of depression and increased likelihood of long-term opioid use). Description of whether associations were strong or weak are noted.
- "Mostly consistent" – At least 75 percent of studies agreed in both direction and statistical significance of association. No more than one study found a statistically significant association in the opposite direction (e.g., that men, not women, were at increased risk of outcome). Remaining studies found no significant association.
    - Note that where three studies evaluated a given association, a determination of "mostly consistent" was not possible.
- "Variable" – Studies are neither consistent nor mostly consistent.

We separately analyzed the studies of identifiable interventions used in (or for) older adults that pertain to the Guiding Questions. These are each described individually.

Findings

Conceptual Framework

The Conceptual Framework (Figure 1) outlines the stages of care for older adults who use (or may use) opioids and factors that impact management decisions and patient outcomes, including assessment of pain, selection of pain treatment, choice of opioid regimen, assessment for opioid misuse or OUD, and management of misuse or OUD. The framework is intended to remain general enough to accommodate the considerable differences among older adults across the population. It incorporates "pathways" by which older adults start using (or misusing) opioids (namely, via a "pain pathway" [**Box A1** in the figure] resulting in opioid prescription by a licensed healthcare professional or via a "recreational use pathway," [**Box A2**] in which people start using opioids for recreational purposes).

For patients who enter through the "pain pathway," (**Box A1**) the clinician first assesses their pain to determine its cause (**Rectangle B**) using appropriate questions and possible screening tools that take into account older adults' characteristics and expectations (e.g., using instruments validated in individuals with dementia to elicit an accurate response, or that overcome the common perception among some older adults that pain is part of the aging process). They then consider possible treatment options (**Rectangle C**). Providers can (or should) use the pain assessment to estimate the risks and benefits of various pain treatments in a given older patient. For example, kidney or liver disease identified during pain assessment influences the relative harms and benefits of using one treatment option versus another, such as nonsteroidal anti-inflammatory drugs versus opioids.

While opioids are an option (**Rectangle C**), nonopioid medications could be used to manage pain among older adults who do not have contraindications; although relative contraindications are commonly present among older adults (e.g., impaired liver or kidney function, hypertension). These medications include acetaminophen, nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen), corticosteroids, antidepressants, antiepileptics, and others (e.g., topical capsaicin products). Nonpharmacological options are available as well and include a wide array of potential interventions, such as yoga, massage therapy, and acupuncture. Since older adults are often more susceptible to adverse drug events than younger adults, nonpharmacological treatment options may offer a lower risk of harms while providing an important benefit to older adults. Importantly, older adults may start "multimodal" treatment (of more than one intervention) that comprises a pain treatment approach that (1) combines medications from different pharmacologic classes and (2) combines pharmacologic and nonpharmacologic therapies or multiple nonpharmacologic therapies.

The framework prioritizes three potential targets to determine factors associated with and interventions for (1) reducing opioid prescriptions where harms outweigh benefits, (2) preventing opioid misuse and OUD, and (3) reducing other opioid-related harms.

Many factors play a role in the decision to use (or avoid using) opioids to manage pain (**Octagon R1**). A key consideration is whether the benefits of opioid treatment outweigh its harms. Such benefit-harm assessments are difficult and can be erroneous when information about key factors is lacking or not considered and can be skewed when there is limited access to effective nonopioid treatment alternatives. Interventions to support benefit-risk assessments (**Triangle I1**) could be employed at this point in the care pathway. For example, patient-level tools could, in theory, help clinicians assess the expected benefits and risks of opioid or other pain treatment use. These may be instruments that predict effectiveness or risks based on easily

assessable factors available to the clinician during the patient encounter. System-level interventions (at the clinic, hospital, pharmacy, healthcare system, or State levels) to increase access to and the affordability of effective nonopioid alternatives may also be impactful.

If opioids are prescribed to an older adult (**Rectangle D**), prescribers must select a dose, schedule, form, and route of administration, and decide if and how they will monitor for opioid effectiveness, adverse events, misuse, and OUD. Age-related changes in metabolism of opioids are pronounced among older adults and clinicians may, for example, need to consider starting an opioid at the lowest tolerated dose (i.e., lower than employed in younger populations) and slowly titrating the dose up to achieve appropriate relief of pain with minimal adverse effects. Opioid use in older adults may eventually result in opioid misuse or OUD, and a variety of factors may predict transition to misuse, OUD, or both (**Octagon R2**). Pharmaceutical, non-pharmaceutical (e.g., behavioral), nonmedical (e.g., educational, community-based), and other interventions could help older adults to safely use prescription opioids and prevent or reduce the risks of transition to opioid misuse and OUD (**Triangle I2**).

If older adults do engage in opioid misuse or develop OUD, the next stage in the care pathway (**Rectangle E**) relates to how misuse or OUD is identified. Similar to the idea that prediction tools could be used to assess likely benefits and harms at the time of opioid prescribing to reduce prescribing where harms outweigh benefits, tools could also help practitioners (and patients) determine who is at increased risk of opioid misuse and OUD. **Rectangle E** is where individuals from the "recreational use pathway" (**Box A2**) may enter into the Conceptual Framework. Identification of misuse or OUD among this group of older adults may require different methods or tools from those used to identify misuse or OUD among those in the "pain pathway."

Older adults identified with opioid misuse or OUD require management to reduce or stop associated harms (**Rectangle F**). Potential management options include interventions to coordinate care or improve healthcare transitions, pharmacological, nonpharmacological, and behavioral treatments, and combinations thereof.

Each care pathway stage (**Rectangles C through F**) may ultimately give rise to an array of factors that predict opioid-related harms other than misuse or OUD (**Octagon R3**). Interventions (**Triangle I3**) could affect the factors that predict opioid-related harms (other than opioid misuse or OUD). If effective, they would prevent opioid-related adverse events and optimize other health outcomes (**Box O)**. Rather than solely preventing harms, some intervention may also improve affected individuals' quality of life, physical and cognitive function, and other outcomes, and ultimately reduce death. Improved knowledge of factors to predict these outcomes could inform an understanding of which interventions (in **Triangle I3**) might be most effective.

As indicated by the light green rectangle that encompasses most of the conceptual framework, there are many interconnected variables or potential predictors (represented by green ovals **P1-P8** at the top of the figure) that influence many aspects of the care management process and associated events, as well as each other. These relationships are too numerous, implicit, and complex to be depicted using arrows in the framework and thus are shown through the shaded rectangle. They include pain type, provider, patient, setting, guidance, and substance use factors (ovals **P3-P8**). Other predictors, included outside the light green rectangle, represent system and societal factors (ovals **P1** and **P2**) outside the scope of this Technical Brief. These are likely to impact opioid use, misuse, and OUD, but are beyond the scope of research considered.

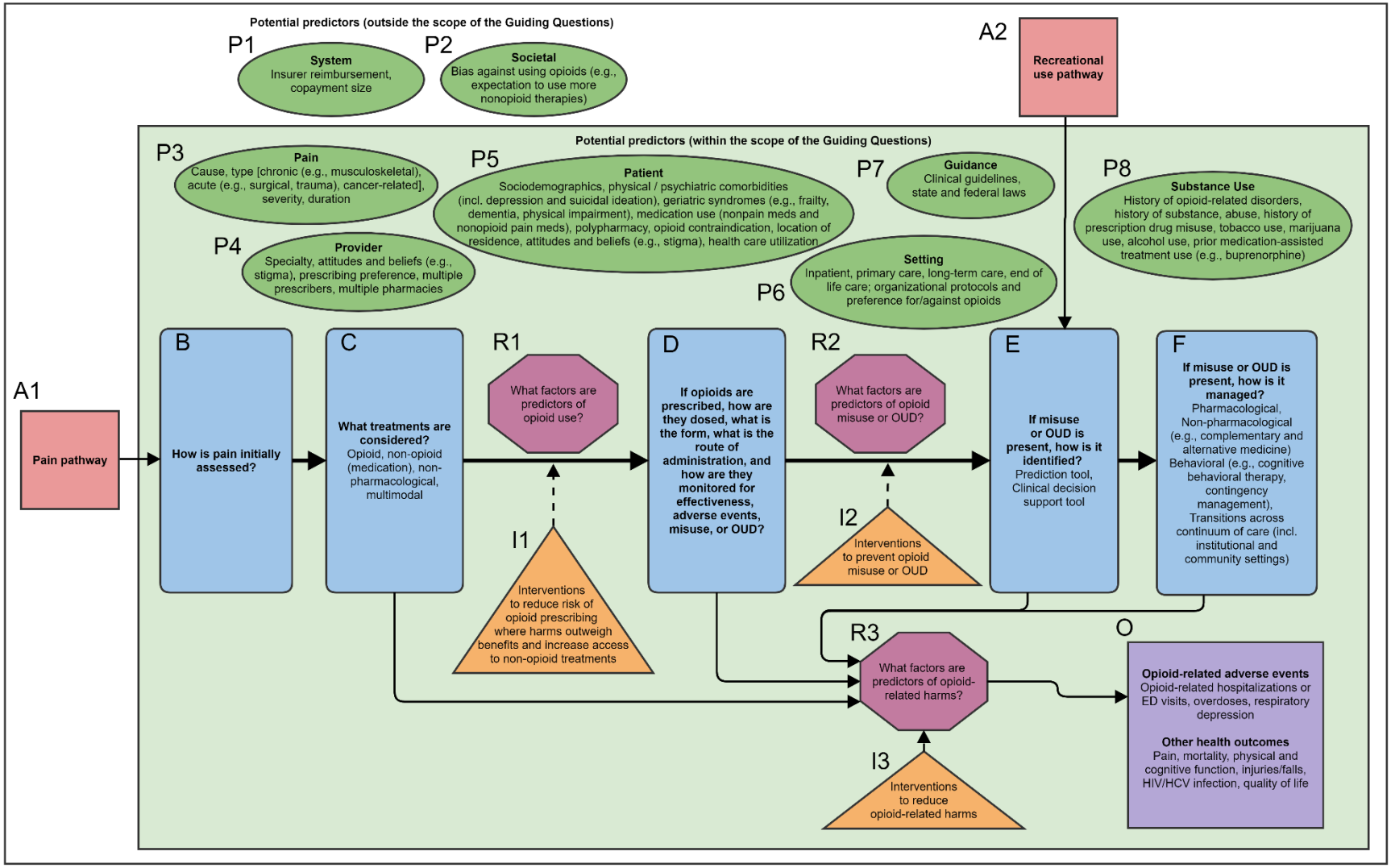
Evidence Map

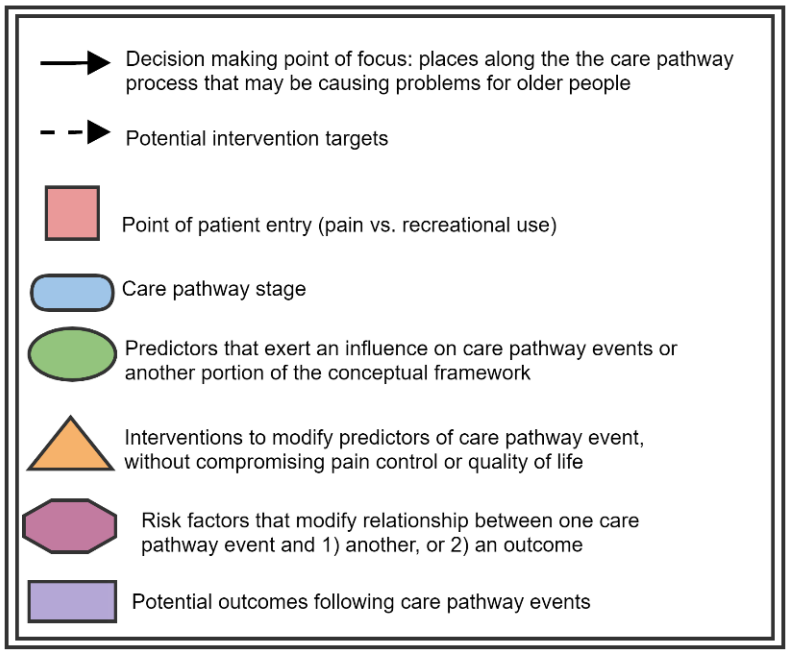
The literature search yielded 6,244 citations, of which 4,153 were screened in duplicate. The remaining citations were predicted to be of low probability of relevance by software. Additional details about screening can be found in Appendix D. Overall, we identified 191 articles of potential interest that addressed associations or interventions. From these, we included 41 studies that reported multivariable analyses of factors associated with outcomes of interest, and 16 studies that evaluated interventions.

Detailed information about these 57 studies are included in Appendix D, Tables D-3 to D-6. Another 121 articles reported unadjusted (univariable) or other analyses and were excluded. Appendix E lists the rejected articles and reasons for rejection. Appendix D (first paragraph) and Appendix Figure D-1 provide further details about the literature flow.

We first present the evidence base of factors independently associated with outcomes of interest followed by the evidence base of relevant interventions.

Figure 1. Conceptual framework





Abbreviations: ED = emergency department, HCV = hepatitis C virus, HIV = human immunodeficiency virus, OUD = opioid use disorder.

Relation of Evidence to Conceptual Framework

Factors Associated With Opioid-Related Outcomes in Older Adults

Overview of Literature

We restricted our review to the 41 studies that reported multivariable analyses, since findings from unadjusted analyses are more likely to be spurious and therefore do not add much to the evidence base (for the purpose of determining likely candidates for independent predictors of outcomes of interest). None of the models (multivariable analyses) was designed or evaluated as a screening or prediction tool.

We organized the 41 studies based on their analyzed outcomes. We categorized these into seven overall types of outcomes:

1. long-term opioid use
2. opioid-related disorders
3. multiple opioid prescribers (or pharmacies)
4. clinical harms, related to either mental or physical health conditions
5. opioid-related hospitalization or ED visit
6. opioid overdose
7. death

This categorization roughly corresponds to the temporal order that people interact with opioid use. Referring to the Conceptual Framework (Figure 1), category 1 aligns with opioid use (Octagon R1), categories 2 and 3 align with opioid misuse or OUD (Octagon R2 and Rectangle E) and categories 4 to 7 align with opioid-related adverse events and other health outcomes (Octagon R3 and Box O).

We also categorized the numerous specific evaluated factors into 31 categories that fell into 9 factor types, which are depicted in the Conceptual Framework (Figure 1) as noted below. These factors are:

- System factors: insurance feature (Oval P1)
- Pain factors: cause and severity (P3)
- Provider factors: specialty (P4)
- Patient factors (P5)
    - Demographics: age, gender, race/ethnicity
    - Socioeconomic factors: income, employment, education, rural vs. urban, social factors, insurance status
    - Health conditions: comorbidities (physical health), mental health, activities of daily living, quality of life, healthcare utilization
    - Pharmaceutical treatments: nonopioid pain treatments, nonpain treatments
- Guidance: opioid stewardship (P7)
- Substance use (past or current): opioid-related disorders (opioid misuse, OUD, high-risk behaviors), methadone use, number of opioid prescribers, substance misuse, tobacco use, benzodiazepine use or misuse (P8)
- Opioid factors: history of opioid use, opioid duration, opioid amount, opioid type, and opioid prescription rates (addressed in Rectangles C and D)

None of the factors evaluated by eligible studies related to societal factors, such as cultural biases for or against using opioids (Oval P2), or setting factors (Oval P6). Some factors that could be categorized as "setting" were categorized as patient factors (e.g., rural vs. urban) or provider factors (e.g., specialty).

Very few analyses reported patient-centered outcomes. More than half (22 of 41) of the multivariable studies evaluated factors independently associated with long-term use of opioids. Many fewer studies evaluated outcomes pertaining to opioid-related harms (such as overdose or OUD) or high-risk or undesirable behaviors (such as opioid misuse). The factors most commonly evaluated included demographic factors, comorbidities, medication factors, history of pain or opioid use, social conditions, and history of substance use. All studies were based on retrospective (already collected) data. Three-quarters of the studies (31 of 41) were longitudinal; 10 were cross-sectional, based on survey or registry data. Most included specific populations of patients (e.g., based on cause of pain, such as surgery or hip fracture), as noted in the tables describing the study findings.

Roadmap for Reading the Description of the Evidence Map

We describe the evidence pertaining to each "predictor" octagon in the Conceptual Framework (Figure 1) separately. Namely, we describe studies pertaining to "predictors" of opioid use (Octagon R1), "predictors" of opioid misuse and OUD (Octagon R2), and "predictors" of opioid-related harms (Octagon R3). While, we had hoped to find studies that evaluated predictors, many of these studies were either cross-sectional or otherwise did not evaluate whether the variables included in their models predicted future events. We use the term "factor" to cover any variable entered into the multivariable models (including true predictors, risk factors, or other measures).

Within each "risk factor" category section (R1, R2, R3), we separately summarize particular categories (and subcategories) of outcomes (e.g., the category Opioid-Related Disorders, with

the subcategories OUD, opioid misuse, and high-risk obtainment of prescription opioids). Within each (sub)section, we describe the evidence and discuss relevant research needs. Additional research needs are discussed at the end of this section on "Factors Associated with Opioid-Related Outcomes in Older Adults."

To help frame the following detailed summaries of the various association studies, in Table 1 we provide an overall summary of the factor-outcome pairs for which there were at least three studies, summarizing findings as well as consistency and strength of association (as defined in the Methods). Outcomes with only one or two studies are not included in Table 1 but are described in the text.

Table 1. Summary of consistency and direction of associations across multivariable analyses

Outcome/Factor	Specific Factor	Strong + Assn	Weak + Assn	Strong − Assn	Weak − Assn	NS	Total	Consistency	Association
Long-term opioid use									
Opioid use	Early (or preoperative)	**7**	2				9	Consistent	Strong (mostly)
Opioid amount	More*	**6**	3				9	Consistent	Strong (mostly)
Pain cause	Back pain	**3**	4				7	Consistent	Strong/weak
Mental health	Depression		11				11	Consistent	Weak
Nonopioid pain treatment	NSAID		4				4	Consistent	Weak
Pain cause	Fibromyalgia		3				3	Consistent	Weak
Benzodiazepine use		**3**	3			1	7	Mostly consistent	Strong/weak
Comorbidities	Comorbidity score †	**2**	4			2	8	Mostly consistent	Strong/weak
Substance misuse	Substance misuse ‡	**2**	7			1	10	Mostly consistent	Weak (mostly)
Tobacco	Tobacco	**1**	4			1	6	Mostly consistent	Weak (mostly)
Income	Low income §		8			2	10	Mostly consistent	Weak
Substance misuse	Alcohol		1			4	5	Mostly consistent	NS
Healthcare utilization	Greater use	**1**				3	4	Mostly consistent	NS
Gender	Female		8	**1**	1	8	18	Variable	
Age	Younger §	**2**	6		2	4	14	Variable	
Race	Black		5		3	4	12	Variable	
Comorbidities	Dementia	**1**	1		2	1	5	Variable	
Geography	Rural/Nonurban		1		1	3	5	Variable	
Opioid type	Long-acting	**2**				1	3	Variable	
Social	Unmarried §	**1**	1			1	3	Variable	
Nonopioid pain treatment	Muscle relaxant		2			1	3	Variable	
Opioid misuse									
Gender	Female		1			2	3	Variable	
Substance misuse	Alcohol	**1**	1			1	3	Variable	

Note: This table includes only factor-outcome pairs that were reported by at least 3 studies. Broad (nonspecific) factor categories (e.g., pain cause) are omitted. Within each outcome, factors are sorted based by consistency, strength of association, and number of studies. Specific factors within broad factor categories are included (i.e., pain cause/back pain, pain cause/fibromyalgia, mental health/depression, nonopioid pain treatment/NSAID, substance misuse/alcohol, race/Black, comorbidities/dementia).

Numbers of studies with strong associations are bolded. Columns are colored only to enhance visualization of directionality of association (see abbreviations list).

Strong association: Measure of association (e.g., relative risk) ≥2.0 (or ≤0.5) and statistically significant.
Weak association: Measure of association between 0.5 and 2.0 and statistically significant.

NS = not statistically significant.
+ = "positive" association (presence or magnitude of factor associated with increased likelihood of outcome).
− = "negative" association (presence or magnitude of factor associated with decreased likelihood of outcome).

Consistent: 100% agreement in direction and statistical significance across studies, irrespective of strength of association.
Mostly consistent: ≥75% agreement (and <100%) across studies, irrespective of strength of association.
Variable: <75% agreement across studies.

Other abbreviations: Assn = association, NSAID = nonsteroidal anti-inflammatory drug.

* Number of prescriptions or opioid dose.
† Charlson Comorbidity Index or Hierarchical Condition Category.
‡ Variably (or not) defined.
§ Note that this factor, and thus the directions of the associations, has been inverted compared with Tables 3 and 4.

Factors Associated With Opioid Use (Octagon R1)

None of the eligible studies evaluated factors associated with opioid use, per se. The largest number of eligible studies evaluated factors associated with long-term opioid use. Long-term opioid use is not a clinical harm in and of itself, since chronic, long-term pain may require long-term analgesia, and thus appropriate long-term opioid use. Evidence from the general population is inconclusive regarding whether long-term opioid use is itself a predictor of opioid misuse or OUD.[67] However long-term opioid exposure likely increases the risk of harm unless appropriately managed, and may indicate persistent pain that is not adequately controlled with other interventions. For these reasons, we determined that it is an outcome of interest.

To help the reader interpret the subsequent summary tables, Table 2 provides a guide to the coding of study findings in Tables 3 to 14. The set of studies that evaluated factors associated with opioid use among older adults are summarized in Tables 3 to 6.

Factors Associated With Long-Term Opioid Use

Evidence Base

More studies evaluated long-term opioid use than all other outcomes combined, possibly because the outcome is relatively easy to gather from pharmacy or insurance records. We found 22 studies that reported multivariable models of long-term opioid use in older adults.[68-89] Definitions of long-term opioid use varied across studies: 11 evaluated at timepoints from 3 to 6 months of use or more, two evaluated 9 to 12 month data, six evaluated approximately 1 year, one evaluated 1 month data, and two did not define long-term opioid use.

In brief, several factor categories (and specific factors) have been found to be associated with increased likelihood of long-term opioid use. Furthermore, many of the associations are strong. Given the large number of specific factors evaluated, to help the reader, in addition to bolding the factor categories, in the text of this section we also underline the specific factor (although, we sometimes bold or underline both factor categories and specific factors within paragraphs to diminish visual clutter).

Demographic Factors Associated With Long-Term Opioid Use

Fourteen studies evaluated **age** (within the cohort of older adults) as a factor associated with long-term use (Table 3). Studies were variable in regard to whether age (within the cohort of

older adults) is associated with increased likelihood of long-term opioid use; however, the majority of studies found (mostly weak) associations between older age and *decreased* likelihood of long-term opioid use. Among 18 studies evaluating **gender**, associations were also variable, but only two found that men were more likely to use opioids long-term. Notably, the only strong association was in a study of people with oropharyngeal cancer that, counter to most others, found that men were twice as likely to have continuous opioid use at 6 months. Twelve studies found variable associations between **race** and likelihood of long-term use, but all associations were weak or nonsignificant. Among the eight studies that reported statistically significant associations, five studies found that Blacks (or other non-White racial groups) had an increased likelihood of long-term opioid use, while three others found an association with decreased likelihood.

Health Status Factors Associated With Long-Term Opioid Use

Seventeen studies evaluated a large range of **comorbidities**, both within and between studies (Table 3). Studies were variable in their findings, but most found that there were associations between at least some comorbidities and the likelihood of long-term opioid use; these associations were mostly weak. The strong associations found were for presence of 3 to 4 comorbidities, Hierarchical Conditional Category ≥1.20, and Charlson Comorbidity Index ≥3 (but four of five studies found weak associations), and, separately, migraine, mild liver disease, and weight loss (not fully defined, but described in the study as a nutritional or medical comorbidity after total hip arthroplasty). A third study found a strong association between an AIDS diagnosis and a *decreased* likelihood of long-term opioid use. The evidence for dementia is variable among five studies: dementia was found to be strongly associated with increased likelihood of long-term use in one study and weakly associated in a second study, but, in contrast weakly associated with *decreased* likelihood in two other studies, and no significant association in the final study.

Four studies of **healthcare utilization** were mostly consistent, with three finding no statistically significant association with likelihood of long-term opioid use (Table 3). The exception found a strong association between "any hospitalization" and increased likelihood of long-term use. Fourteen studies evaluated **mental health** factors. Eleven of these studies were consistent in finding weak associations between depression and increased likelihood of long-term opioid use. Only psychosis, in a single study, was found to be strongly associated with increased likelihood of long-term opioid use. Three studies reported that people with schizophrenia or bipolar disease were less likely to use opioids long-term.

Socioeconomic and Related Factors Associated With Long-Term Opioid Use

Ten studies evaluated measures of **income** as factors associated with long-term opioid use (Table 4). Although definitions of income status varied, the 10 studies were mostly consistent, with eight of the studies finding weak associations between higher income and *decreased* likelihood of long-term opioid use. Five studies evaluated **geographic location** (categorized as rural in the table). The studies had variable findings. One study found that urban residents were (weakly) more likely to have long-term opioid use than "metropolitan" residents (they found no statistically significant association with rural residents). One found that nonurban residents were (weakly) more likely to have long-term opioid use. The other three studies found no statistically significant association with metropolitan residence.

Four studies evaluated **social** factors (Table 4). Three studies evaluated marital status, finding, in turn, strong, weak, and no statistically significant associations between being

unmarried and increased likelihood of long-term opioid use. The fourth study found that whether people dwelled in their home was not associated with long-term use. Two studies evaluated **insurance** status, with one study finding a weak association between Medicare Advantage coverage and increased likelihood of long-term opioid, relative to standard Medicare coverage and the second study founding a weak association between having supplemental Medicare coverage with relatively more copayments or deductibles, compared with coverage plans with minimal copayments or deductibles.

Pain Factors Associated With Long-Term Opioid Use

Nineteen studies evaluated a variety of **causes of pain** (Table 5). In brief, a large number of specific causes were associated with long-term use. The six strong associations found were mostly musculoskeletal conditions: back pain (in three studies, one with the strong association specifically for chronic back pain), bilateral total knee arthroplasty (TKA) (vs. unilateral TKA), and osteoporosis. One study found a strong association of long-term opioid use with higher than "very low" risk category of prostate cancer after radical prostatectomy. Two specific causes of pain were evaluated by at least three studies, each with consistent findings. Long-term opioid use was associated with back pain in seven studies (three strong [just chronic back pain in one study], three weak associations [just new back pain in one study]) and with fibromyalgia in three studies (all weak)

Prescription Drug Treatment Factors Associated With Long-Term Opioid Use

Seven studies evaluated (concomitant) **nonopioid pain treatments** as factors associated with long-term opioid use (Table 5). It should be noted that the concomitant use of nonopioid pain treatments may be a marker of less-well controlled chronic pain. The most frequently analyzed nonopioid pain treatment was nonsteroidal anti-inflammatory drugs (NSAIDs). The four studies were consistent in finding weak associations between NSAID use and long-term opioid use. Across the studies, the three strong associations were found with acetaminophen use (in one study), with antineuropathic pain treatments (either antidepressants or antiepileptics, in one study), and with muscle relaxants (in one study, but only weak associations in two other studies). Seven studies evaluated a variety of **nonpain treatments**. Individual studies found weak associations with rheumatoid arthritis treatments, anxiolytics, antipsychotics, sleep medication, and radiation and chemotherapy treatments.

Opioid Use Factors Associated With Long-Term Opioid Use

Nine studies evaluated different measures of **opioid use** as factors associated with long-term opioid use (Table 5). The studies consistently found that prior use (including preoperative use) or early use after surgery or an injury were associated with increased likelihood of long-term opioid use; seven of the nine studies found strong associations. Two studies disagreed regarding dependence as an associated factor. Neither study defined "dependence." One study found a weak association between dependence as an independent variable and opioid use 9 to 12 months postoperatively (as the dependent variable). The second study, counterintuitively, reported that people with opioid dependence (as a comorbidity) were almost half as likely to be using opioids 9 to 12 months postoperatively. No explanation for this finding was given. In contrast, nine studies were consistent in finding that increased **opioid amounts** (more prescriptions or higher dose opioids) were associated with long-term use (strong associations in six of the studies). This association was found for greater number of prescriptions (five studies), higher dose (three studies), and overlap of opioid prescriptions (one study).

Four studies evaluated different **opioid types** (Table 5), both within and across studies. Three studies evaluated long-acting opioids, with different findings of either a strong (2 studies) or no association (1 study) with long-term opioid use. One study found a strong association specifically for use of the strong opioid oxycodone (compared with the weak opioid hydrocodone) with long-term opioid use, while another found only a weak association with the use of strong opioids (see Table 5 footnote). Another study found a strong association between use of the weak opioid tramadol (versus no tramadol) and long-term opioid use, while one study found no statistically significant associations with use of the weak opioid codeine. Finally, one study found that transdermal opioids were strongly associated with increased likelihood of long-term use.

Substance Use and Misuse Factors Associated With Long-Term Opioid Use

A single study reported that **methadone** users were at strongly increased likelihood of long-term use (Table 6). Fourteen studies evaluated (at least implicitly nonopioid) **substance misuse** as factors associated with long-term opioid use. The studies were variable in their findings, with ten finding (mostly weak) associations between substance (or "drug") use (or "abuse"; mostly not specifically defined) and long-term opioid use, but four finding no significant association. However, most of the associations with specific substances were not statistically significant. In particular, five studies were mostly consistent in finding no significant association with alcohol "abuse", with only one study finding a weak association. This study was also the only study to evaluate use of marijuana, cocaine, and amphetamines, finding that marijuana use was weakly associated with increased likelihood of long-term opioid use, but there were nonsignificant associations with cocaine and amphetamine use.

Six studies evaluated **tobacco use** as a factor associated with long-term opioid use (Table 6). The studies were mostly consistent (5 of 6 studies) in finding that people who used tobacco had increased likelihood of long-term opioid use, but only one of the studies found a strong association. Seven studies were mostly consistent that people who used **benzodiazepines** also had increased likelihood of long-term opioid use. Three of these seven studies found strong associations, but one found no statistically significant association.

Two studies evaluated proxy measures for **opioid stewardship** (Table 6). One found a strong association between prescribers being concordant with guidance and decreased likelihood of long-term opioid use. Based on evaluation of a claims database,[78] the study found that those participants (not seen in an ED) whose opioid prescriptions were for no more than 3 days, no more than 50 mean morphine equivalents, and were not for a long-acting opioid were less than one-fourth as likely to use opioids for at least 12 months than patients who received regimens with a longer duration, higher dose, or use of a longer-acting opioid. A similar, but weak association, was found for those participants seen in the ED. In the second study,[81] participants whose medical records indicated that they were provided with any type of tapering plan for their opioids had a (weakly) decreased likelihood of long-term opioid use. Neither study evaluated opioid stewardship as an intervention, per se.

Summary of Factors Associated With Long-Term Opioid Use

Overall, 22 multivariable models have evaluated a large number of potential factors associated with long-term opioid use among older adults. Table 1 highlights the findings for factor-outcome pair associations analyzed by at least three studies.

Studies were consistent (in full agreement) that—in nine studies—opioid use prior to surgery or injury (or early use after surgery) and—in nine studies—greater amount of opioids (more

prescriptions or higher dose) are the factors with mostly strong associations with long-term opioid use.

Other consistent associations, but with largely weak associations, were found with back pain (7 studies, 3 with strong associations), depression (11 studies, all weak associations), concomitant NSAID use (4 studies, all weak associations), and fibromyalgia (3 studies, all weak associations).

Studies were mostly consistent (≥75% agreement) that benzodiazepine use (6 of 7 studies, 3 with a strong associations), comorbidity scores (6 of 8 studies, 2 with strong associations), variably or undefined substance misuse (9 of 10 studies, 2 with strong associations), tobacco use (5 of 6 studies, 1 with a strong association), and low income (8 of 10 studies, all with weak associations) were associated with long-term opioid use.

Studies were also mostly consistent that alcohol "abuse" (4 of 5 studies) and healthcare utilization (3 of 4 studies) were *not* associated with long-term opioid use; however, one of these latter studies found a strong association between "any hospitalization" and long-term use.

Factors with variable findings of association (evaluated by at least 3 studies) included gender (8 of 18 studies found weak associations with female gender; 2 found associations with male gender, 1 strong), age among older adults (8 of 14 studies found mostly weak associations with relatively younger age; 2 found weak associations with older age), Black race (8 of 12 found weak associations, but 5 associations were with increased and 3 were with decreased likelihoods), dementia (2 each, among 5 studies found associations with increased and with decreased likelihood), rural or non-urban residence (1 each, among 5 studies found associations with increased and with decreased likelihood), prescription of long-acting opioids (2 of 3 with studies found associations, both strong), unmarried relationship status (2 of 3 studies found associations, 1 strong), and use of muscle relaxants (2 of 3 studies found weak associations).

Research Needs on Predictors of Long-Term Opioid Use

The ability to predict which patients are more likely to use opioids long-term might help with management and harm prevention. However, more research is needed to determine how to identify these patients. In particular, additional research regarding how specific comorbidities, social determinants of health, insurance features (type, status), use of specific treatments for indications other than pain, specific opioid types and methadone, and opioid stewardship programs relate to long-term opioid use would be of value. More research is also needed to understand the role of stress, anxiety, depression, trauma, and other behavioral and mental health conditions in increasing the likelihood of long-term opioid use. Multimorbidity and associated polypharmacy have much higher prevalence rates in older adults and deserve attention as potential predictors.

However, future studies would be more useful if they distinguished between problematic long-term opioid use (e.g., misuse, psychological dependence) and long-term use due to otherwise poorly controlled pain. Older adults with problematic opioid use may need interventions to reduce opioid use, whereas those with uncontrolled pain may require other interventions to better treat the underlying condition or other modalities of pain management. Specifically, research on how to successfully taper opioids, especially after long-term use, is also critically needed. Future studies should focus in particular on which factors are associated with the inability to taper opioids, including opioid dose, duration of opioid use, mental health conditions, and any prior history of substance use disorders.

Table 2. Code to interpret heat maps of multivariable analyses (in Tables 3 to 14)

Color*	Symbol	Strength of Association	Direction of Association	Statistical Significance	Factor Type	Measure of Association Value
Bright pink	⬆	Strong	Factor present associated with *higher* risk of outcome	P<0.05†	Categorical	≥2
Light orange	↑	Weak	Factor present associated with *higher* risk of outcome	P<0.05†	Categorical	<2
Light pink	△	"Positive"	*Higher* value of factor associated with *higher* risk of outcome	P<0.05†	Continuous	Any
Bright blue	⬇	Strong	Factor present associated with *lower* risk of outcome	P<0.05†	Categorical	≤0.5
Light blue	↓	Weak	Factor present associated with *lower* risk of outcome	P<0.05†	Categorical	>0.5
Middle blue	▽	"Negative"	*Higher* value of factor associated with *lower* risk of outcome	P<0.05†	Continuous	Any
Grey	NS	None	No association between factor and outcome	P≥0.05†	Any	Any
Light yellow	None	Mixed	Variable within study, as indicated	Mixed	Any	Mixed

* Note that color coding does not provide unique information in addition to the text provided within the heat map tables.
† Or as defined by study authors.

Table 3. Heat map of multivariable analyses of demographic and health status factors and long-term opioid use*

Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Age	Gender	Race	Comorbidity	HC Util	Mental Health
Al Dabbagh 2016 26707940[68] Longitudinal retrospective (femoral fracture)	Earlier discontinuation of opioid prescriptions (undefined) † 75 years (16-102)	↓ (Older)	NS				
Brescia 2019 31447051[70] Longitudinal retrospective (general population)	New persistent long-term use (91-180 days) 71 years (NR, Medicare)	NS	↓ (Female)	↑ Black	↑ Charlson CI, others		↓ (Schizo-phrenia)
Cancienne 2018 28887020[71] Longitudinal retrospective (TKA)	Prolonged postoperative opioid use (3-6 months) NR (89% ≥60)		NS	↓ (Black)	↑ Obesity		↑ Depression
Curtis 2017 28635179[72] Longitudinal retrospective (rheumatoid arthritis)	Long-term opioid use (undefined) 67 years (NR, Medicare)	▽ (Older)	↓ (Female)	↑ Black	↑↓ Multiple (Multiple) ‡	⬆ Hospitalization [DME weak]	↑ Depression Anxiety
Daoust 2018 28767563[73] Longitudinal retrospective (trauma)	Opioid use 1 year after injury 79 years (>65)		↑ Female			NS	↑ Depression
Hadlandsmyth 2018 28927564[74] Longitudinal retrospective (TKA)	Opioid use at 12 months 66 years (NR)	NS	NS	NS	NS [Dementia NR]	NS	NS [Depression NR]
Hamina 2017 28092324[75] Longitudinal retrospective (Alzheimer disease)	Long-term opioid use (6 months) 80 years (NR)	↑ Older	↑ Female		↑ Multiple, Including dementia		
Inacio 2016 27130165[76] Longitudinal retrospective (THA)	New chronic opioid use (3-4 months) 80 years (NR)		↑ Female		⬆ Multiple § Dementia		↑ Depression
Jain 2018 29561298[77] Longitudinal retrospective (lumbar fusion for degenerative disease of the spine)	Long-term opioid use (12 months) 66 years (NR)	⬇ (Older)	↑ Female	↑ Black			↑ Depression Anxiety
Karttunen 2019 30370943[79] Longitudinal retrospective (general population)	Prolonged opioid use (3 months) 80 years (NR)	↓ (Older)			↑↓ Multiple (Alzheimer)		↑↓ Depression or bipolar (Schizo-phrenia)
Lalic 2018 29451672[80] Longitudinal retrospective (without cancer)	Opioid persistence (12 months) NR (≥65 years) **		NS		⬆ 3-4 comorbidities		⬆ Psychosis [Depression, weak]

Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Age	Gender	Race	Comorbidity	HC Util	Mental Health
Lindestrand 2015 25952252[81] Longitudinal retrospective (hip fracture)	Persistent opioid use (3-6 months) 82 years (NR)	NS	NS		NS (including dementia)	NS	
Loeb 2020 31584849[82] Longitudinal retrospective (prostate cancer)	New chronic opioid use (>2 months) 64 years (NR)				↑ Charlson CI ≥3		
McDermott 2019 30396321[83] Longitudinal retrospective (oropharyngeal cancer)	Continuous opioid use at 6 months NR (≥66 years)	↓ (Older)	↓ (Female)	NS	NS (Dementia NR)		
Musich 2019 30401575[84] Longitudinal retrospective (general population)	Chronic opioid use >90 days 76 years (≥65)	↑↓ ≥85 (70-79)	↑ Female	NS	↑ HCC score		↑ Depression, anxiety
Namba 2018 29753617[85] Longitudinal retrospective (TKA)	Number of prescriptions days 271-360 postoperative 68 years (NR)	NS	NS	↑↓ Black (Asian)	↑/↓ Multiple, weak (AIDS, strong) (Dementia, weak)		↑↓ Depression, others (Bipolar)
Nelson 2020 31445908[86] Longitudinal retrospective (lung resection for NSCLC)	Persistent opioid use (3-6 months) NR (≥66 years)	↓ (Older)	NS	NS	↑ Charlson CI		
Rao 2018 29891412[87] Longitudinal retrospective (shoulder arthroplasty)	Opioid use days 271-360 postoperative NR (84% ≥60 years)		↑ Female	↓ (Black)	↑ ASA Class ≥3 Neurodegenerative		↑ Depression Anxiety
Santosa 2020 31349994[88] Longitudinal retrospective (surgery)	New persistent opioid use (6 months) NR (≥65 years)	NS	NS	↑↓ Black (Non-White, Non-Black)	↑ Charlson CI [Prior anticoagulant NS]		↑ Mood disorder, suicidality [Anxiety, others NS]
Shah 2019 31026356[89] Longitudinal retrospective (cancer)	Prolonged opioid prescribing (3 months) 77 years (≥66)	↓ (Older)	↑ Female	↓ (Non-White)	↑ Cancer Charlson CI		↑ Depression

Note: The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article and the strength and direction of the association, as described in Table 2. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., females were at increased risk of opioid use 1 year after injury). Downward arrows are accompanied by text (in parentheses) that indicates the factor that is at *decreased* risk for the outcome, in keeping with the direction of the arrow (e.g., people in older age categories at *decreased* risk of long-term opioid use). In the Comorbidity column, dementia is also highlighted since it frequently, but not universally, was associated with decreased risk, in contrast with other comorbidities.

Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. Studies are presented in alphabetical order.

Abbreviations: ASA = American Society of Anesthesiologists, Charlson CI = Charlson Comorbidity Index (Score), DME = durable medical equipment use, HCC = Hierarchical Condition Category, HC Util = healthcare utilization, NR = not reported, NSCLC = nonsmall cell lung cancer, PMID = PubMed identifier, THA = total hip arthroplasty, TKA = total knee arthroplasty.

* 2 studies that evaluated long-term opioid use did not evaluate the factors in this table: Alam 2012 (PMID 22412106), Jeffrey 2018 (PMID 28967517).
† Note that this outcome is of short, not prolonged, duration of use. The arrows in this row are consistent with other studies (up arrows indicated increased risk of *not* early discontinuation).
‡ Seven medical conditions were weakly associated with increased risk. Three medical conditions were weakly associated with decreased risk.
§ Migraine, mild liver disease, weight loss.
** In reported subgroup analysis.

Table 4. Heat map of multivariable analyses of socioeconomic and related factors and long-term opioid use*

Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Income	Rural	Social	Insurance
Brescia 2019 31447051[70] Longitudinal retrospective (general population)	New persistent long-term use (91-180 days) 71 years (NR, Medicare)	↑ Dual MCare/MCaid eligible			
Curtis 2017 28635179[72] Longitudinal retrospective (rheumatoid arthritis)	Long-term opioid use (undefined) 67 years (NR, Medicare)	↓ (High income)			
Hamina 2017 28092324[75] Longitudinal retrospective (Alzheimer disease)	Long-term opioid use (6 months) 80 years (NR)	↓ (High SES)			
Jain 2018 29561298[77] Longitudinal retrospective (lumbar fusion for degenerative disease of the spine)	Long-term opioid use (12 months) 66 years (NR)				↑ MCare Advantage
Karttunen 2019 30370943[79] Longitudinal retrospective (general population)	Prolonged opioid use (3 months) 80 years (NR)	↓ (High SES)			
Lalic 2018 29451672[80] Longitudinal retrospective (without cancer)	Opioid persistence (12 months) NR (≥65 years) †	↓ (No subsidy)			
Lindestrand 2015 25952252[81] Longitudinal retrospective (hip fracture)	Persistent opioid use (3-6 months) 82 years (NR)			NS	
Loeb 2020 31584849[82] Longitudinal retrospective (prostate cancer)	New chronic opioid use (>2 months) 64 years (NR)			↓ (Married)	
McDermott 2019 30396321[83] Longitudinal retrospective (oropharyngeal cancer)	Continuous opioid use at 6 months NR (≥66 years)	NS	NS	⬇ (Married)	
Musich 2019 30401575[84] Longitudinal retrospective (general population)	Chronic opioid use >90 days 76 years (≥65)	↓ (High income)	↑ Non-urban		↓ ("Medium" coverage, vs. "high")
Nelson 2020 31445908[86] Longitudinal retrospective (lung resection for NSCLC)	Persistent opioid use (3-6 months) NR (≥66 years)	NS	NS	NS	
Santosa 2020 31349994[88] Longitudinal retrospective (surgery)	New persistent opioid use (6 months) NR (≥65 years)	↓ (Not MCaid eligible)	NS		
Shah 2019 31026356[89] Longitudinal retrospective (cancer)	Prolonged opioid prescribing (3 months) 77 years (≥66)	↓ (Not MCaid eligible)	↓ (Non-urban)		

Note: See Table 2 for description of association coding and Table 3 for additional legend information.

Abbreviations: MCaid = Medicaid, MCare = Medicare, NS = not statistically significant, NSCLC = nonsmall cell lung cancer, PMID = PubMed identifier, SES = socioeconomic status.

* 9 studies that evaluated long-term opioid use did not evaluate the factors in this table: Al Dabbagh 2016 (PMID 26707940), Alam 2012 (PMID 22412106), Cancienne 2018 (PMID 28887020), Daoust 2018 (PMID 28767563), Hadlandsmyth 2018 (PMID 28927564), Inacio 2016 (PMID 27130165), Jeffrey 2018 (PMID 28967517), Namba 2018 (PMID 29753617), Rao 2018 (PMID 29891412).

† In reported subgroup analysis.

Table 5. Heat map of multivariable analyses of pain, prescription drug, and opioid use factors and long-term opioid use*

Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Pain Cause	Nonop Pain Tx	Nonpain Tx	Opioid Use	Opioid Dependence	Opioid Amount	Opioid Type
Al Dabbagh 2016 26707940[68] Longitudinal retrospective (femoral fracture)	Earlier discontinuation of opioid prescriptions (undefined) † 75 years (16-102)	NS (injuries)						
Alam 2012 22412106[69] Longitudinal retrospective (short-stay surgery)	Opioid use ~10-14 months postoperative 76 years (≥66)				↑ Early use			
Brescia 2019 31447051[70] Longitudinal retrospective (general population)	New persistent long-term use (91-180 days) 71 years (NR, Medicare)	↑ Back pain, arthritis, lung resection, other			⬆ Pre-op		△ MME	
Cancienne 2018 28887020[71] Longitudinal retrospective (TKA)	Prolonged postoperative opioid use (3-6 months) NR (89% ≥60)	↑ Back pain, fibromyalgia, migraine	↑ Muscle relaxant	↑ Anxiolytic	⬆ Pre-op		⬆ Rxs	
Curtis 2017 28635179[72] Longitudinal retrospective (rheumatoid arthritis)	Long-term opioid use (undefined) 67 years (NR, Medicare)	⬆ Back pain [Cancer, rheumatic weak]	↑ NSAID	↑ Bio-DMARD				
Daoust 2018 28767563[73] Longitudinal retrospective (trauma)	Opioid use 1 year after injury 79 years (>65)	↑ Various injuries			⬆ Early use		⬆ Rxs	
Hadlandsmyth 2018 28927564[74] Longitudinal retrospective (TKA)	Opioid use at 12 months 66 years (NR)	⬆ Bilateral TKA	↑ Muscle relaxant	NS (various)	↑ Pre-op			

Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Pain Cause	Nonop Pain Tx	Nonpain Tx	Opioid Use	Opioid Dependence	Opioid Amount	Opioid Type
Hamina 2017 28092324[75] Longitudinal retrospective (Alzheimer disease)	Long-term opioid use (6 months) 80 years (NR)	↑ Multiple skeletal						
Inacio 2016 27130165[76] Longitudinal retrospective (THA)	New chronic opioid use (3-4 months) 80 years (NR)	⬆ Back pain	⬆ Antidepressant or antiepileptic	NS (various)				
Jain 2018 29561298[77] Longitudinal retrospective (lumbar fusion for degenerative disease of the spine)	Long-term opioid use (12 months) 66 years (NR)	↑ Arthritis			⬆ Pre-op			
Karttunen 2019 30370943[79] Longitudinal retrospective	Prolonged opioid use (3 months) 80 years (NR)	↑ RA, cancer						
Lalic 2018 29451672[80] Longitudinal retrospective (without cancer)	Opioid persistence (12 months) NR (≥65 years) ‡		⬆ Acetaminophen [NSAID, pregabalin weak]	NS (stimulants)			⬆ MME	⬆ Trans-dermal § Strong opioids **
Lindestrand 2015 25952252[81] Longitudinal retrospective (hip fracture)	Persistent opioid use (3-6 months) 82 years (NR)	⬆ Osteoporosis			⬆ Pre-op			
Loeb 2020 31584849[82] Longitudinal retrospective (prostate cancer)	New chronic opioid use (>2 months) 64 years (NR)	⬆ Prostate cancer risk category						
McDermott 2019 30396321[83] Longitudinal retrospective (oropharyngeal cancer)	Continuous opioid use at 6 months NR (≥66)	NS (Cancer-related)			⬆ Prior		⬆ High-dose	⬆NS Oxycodone [Codeine, long-acting NS]
Musich 2019 30401575[84] Longitudinal retrospective (general population)	Chronic opioid use >90 days 76 years (≥65)	⬆↓ Chronic back pain [Weak: new back pain] (Trauma) [NS: TKA]	⬆ Muscle relaxant [NSAID, PT weak]	↑ Antipsychotic, sleep drug				⬆ Long-acting, tramadol

Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Pain Cause	Nonop Pain Tx	Nonpain Tx	Opioid Use	Opioid Dependence	Opioid Amount	Opioid Type
Namba 2018 29753617[85] Longitudinal retrospective (TKA)	Number of prescriptions days 271-360 postoperative 68 years (NR)	↑↓ Back pain, fibromyalgia, others (Carpal tunnel, joint pain)	↑ NSAID			↓ (Dependence)	△ Rxs	
Nelson 2020 31445908[86] Longitudinal retrospective (lung resection for NSCLC)	Persistent opioid use (3-6 months) NR (≥66 years)	↑ Open lung surgery [vs. thorascopic surgery]		↑ Cancer treatment types				
Rao 2018 29891412[87] Longitudinal retrospective (shoulder arthroplasty)	Opioid use days 271-360 postoperative NR (84% ≥60 years)	↑↓ Fibromyalgia multiple musculoskeletal (Fracture, Limb pain)				↑ Dependence	⬆ Rxs	
Santosa 2020 31349994[88] Longitudinal retrospective (surgery)	New persistent opioid use (6 months) NR (≥65 years)	↑ Back pain, major surgery			↑ Pre-op		⬆ Opioid overlap † †	⬆ Long-acting
Shah 2019 31026356[89] Longitudinal retrospective (cancer)	Prolonged opioid prescribing (3 months) 77 years (≥66)	↑ Lung cancer ⌗⌗			⬆ Prior		↑ MME, Rxs	

Note: See Table 2 for description of association coding and Table 3 for additional legend information.

Abbreviations: Bio-DMARD = biologic disease-modifying antirheumatic drug, MME = mean morphine equivalents, Nonop Pain Tx = nonopioid pain treatment (use of), Nonpain Tx = nonpain treatment (use of), NS = not statistically significant, NSAID = nonsteroidal anti-inflammatory drug, NSCLC = nonsmall cell lung cancer, PMID = PubMed identifier, Pre-op = preoperative use, PT = physical therapy, Rxs = (larger number of) prescriptions, RA = rheumatoid arthritis, THA = total hip arthroplasty, TKA = total knee arthroplasty (replacement)

* 1 study that evaluated long-term opioid use did not evaluate the factors in this table: Jeffrey 2018 (PMID 28967517).

† Note that this outcome is of short, not prolonged, duration of use. The arrows in this row are consistent with other studies (up arrows indicated increased risk of *not* early discontinuation).

‡ In reported subgroup analysis.

§ # The study also found a weak association with use of strong opioids.

** Strong opioids included: morphine, oxycodone, buprenorphine, fentanyl, hydromorphone, and methadone. Weak opioids included single-ingredient codeine, combination codeine preparations, tramadol, and tapentadol.

†† 2 prescriptions whose days' supplies overlap by ≥7 days.

‡‡ Versus prostate cancer.

Table 6. Heat map of multivariable analyses of substance use or misuse and related factors and long-term opioid use*

Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Methadone	Substance Misuse	Tobacco	Benzo	Opioid Stewardship
Brescia 2019 31447051[70] Longitudinal retrospective (general population)	New persistent long-term use (91-180 days) 71 years (NR, Medicare)		↑ Substance use	↑ Tobacco		
Cancienne 2018 28887020[71] Longitudinal retrospective (TKA)	Prolonged postoperative opioid use (3-6 months) NR (89% ≥60)	⬆ Methadone use	↑ Alcohol abuse, marijuana use [Cocaine use, amphetamine use NS]	↑ Tobacco		
Daoust 2018 28767563[73] Longitudinal retrospective (trauma)	Opioid use 1 year after injury 79 years (>65)		NS (Alcoholism)			
Hadlandsmyth 2018 28927564[74] Longitudinal retrospective (TKA)	Opioid use at 12 months 66 years (NR)		↑ Substance use		NS	
Hamina 2017 28092324[75] Longitudinal retrospective (Alzheimer disease)	Long-term opioid use (6 months) 80 years (NR)		↑ Substance abuse		↑ Benzo	
Inacio 2016 27130165[76] Longitudinal retrospective (THA)	New chronic opioid use (3-4 months) 80 years (NR)		NS (Alcohol abuse)		↑ Benzo	
Jain 2018 29561298[77] Longitudinal retrospective (lumbar fusion for degenerative disease of the spine)	Long-term opioid use (12 months) 66 years (NR)		⬆ Drug abuse	↑ Tobacco		
Jeffrey 2018 28967517[78] Longitudinal retrospective (general population)	Long-term opioid use (12 months) 73 years (NR, Medicare)					⬇ (Guideline concordant) †
Karttunen 2019 30370943[79] Longitudinal retrospective	Prolonged opioid use (3 months) 80 years (NR)		↑ Substance abuse		⬆ Benzo	
Lalic 2018 29451672[80] Longitudinal retrospective (without cancer)	Opioid persistence (12 months) NR (≥65 years) ‡		NS (Alcohol dependence)	↑ Tobacco	↑ Benzo	
Lindestrand 2015 25952252[81] Longitudinal retrospective (hip fracture)	Persistent opioid use (3-6 months) 82 years (NR)					↓ (Tapering plan) §

Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Methadone	Substance Misuse	Tobacco	Benzo	Opioid Stewardship
McDermott 2019 30396321[83] Longitudinal retrospective (oropharyngeal cancer)	Continuous opioid use at 6 months NR (≥66)		NS (Alcohol or substance abuse)	⬆ Tobacco		
Musich 2019 30401575[84] Longitudinal retrospective (general population)	Chronic opioid use >90 days 76 years (≥65)				⬆↑↓ Benzo [vary by timing of use]	
Namba 2018 29753617[85] Longitudinal retrospective (TKA)	Number of prescriptions days 271-360 postoperative 68 years (NR)		↑ Substance abuse			
Rao 2018 29891412[87] Longitudinal retrospective (shoulder arthroplasty)	Opioid use days 271-360 postoperative NR (84% ≥60 years)		↑ Substance abuse			
Santosa 2020 31349994[88] Longitudinal retrospective (surgery)	New persistent opioid use (6 months) NR (≥65 years)		↑ Alcohol or substance abuse	NS	⬆ Benzo	
Shah 2019 31026356[89] Longitudinal retrospective (cancer)	Prolonged opioid prescribing (3 months) 77 years (≥66)		⬆ Drug abuse [Alcohol abuse NS]			

Note: See Table 2 for description of association coding and Table 3 for additional legend information.

Abbreviations: Benzo = benzodiazepine use, NS = not statistically significant, PMID = PubMed identifier, THA = total hip arthroplasty, TKA = total knee arthroplasty.

* 5 studies that evaluated long-term opioid use did not evaluate the factors in this table: Al Dabbagh 2016 (PMID 26707940), Alam 2012 (PMID 22412106), Curtis 2017 (PMID 28635179), Loeb 2020 (PMID 31584849), Nelson 2020 (PMID 31445908).
† Administrative claims database determination that prescriptions were for ≤3 days, ≤50 mean morphine equivalents/day, and not a long-acting opioid.
‡ In reported subgroup analysis.
§ Nonspecific tapering plan, based off of chart review.

Factors Associated With Opioid-Related Disorders (Octagon R2)

Six studies evaluated factors associated with opioid-related disorders (Tables 7 to 9). Two additional studies looked at predictors that older adults would receive opioid prescriptions from multiple opioid prescribers (Table 10). Although having multiple prescribers does not by itself indicate a disorder, it does indicate potential lack of coordination and therefore increased risk of harm to the patient.

Factors Associated With Opioid-Related Disorders

Evidence Base

Six studies reported multivariable models of factors associated with opioid-related disorders, including opioid use disorder (OUD), opioid misuse, and high-risk obtainment of prescription opioids (Tables 7 to 9).[90-95] The models evaluated a large number of factors related to demographics, patient health status, socioeconomic and related factors, insurance status, pain factors, opioid use factors, and substance use/misuse.

Factors Associated With Opioid Use Disorder

Only one study evaluated the risk of OUD, finding that the strongest factors were **mental health** (anxiety disorder; Table 7), **pain severity** ("interference," whether one's pain interferes with daily activities; Table 9), and other **substance misuse** (both marijuana and alcohol; Table 9). The study also found evidence that younger **age** and Hispanic **ethnicity** (Table 7), being unemployed (Table 8), and using tobacco (Table 9) are associated with increased risk of OUD.

Factors Associated With Opioid Misuse

Four studies evaluated opioid misuse (or "abuse"; note: the original wording of the studies is maintained to avoid misrepresenting the original studies, even if the language used by the authors might currently be considered inappropriate or stigmatizing). Substance misuse and gender were the only factors evaluated by at least three studies. Three studies had variable findings regarding **substance misuse**, specifically alcohol (Table 9): one study found a strong association between a history of an alcohol-related healthcare visits and opioid misuse, another found a statistically significant association between higher scores on the CAGE Questions for Alcohol Use and misuse, but a third study found no statistically significant association between hazardous drinking and opioid misuse. Three studies also had variable findings regarding **gender** (Table 7): one study found a weak association that women were at increased risk of opioid use, but the other two found no statistically significant difference between genders.

Rural versus urban residence was evaluated by two studies, both of which found no association (Table 8). Among the other factor categories evaluated by two studies (**age**, **comorbidities**, **mental health conditions** [Table 7], **cause of pain**, and **pain severity** [Table 9], in all cases one study found a statistically significant association and the second study found no statistically significant association). Other factors were evaluated by only a single study.

Factors Associated With High-Risk Behaviors

One study evaluated high-risk obtainment of prescription opioids as an outcome. The study found strong associations for older **age** (≥65, at various thresholds vs. 60-64; Table 7), college **education** (Table 8), and **opioid misuse** (recreational use; Table 9). Increased associations were also found for **women** (Table 7) and people with less **social** connectedness (Table 8). No

statistically significant associations were found for **quality of life** (Table 7) or **tobacco use** (Table 9).

Summary of Factors Associated With Opioid-Related Disorders

Six studies have evaluated factors associated with opioid-related disorders among older adults, including OUD, opioid misuse, and high-risk behaviors, but since the researchers largely analyzed different sets of factors, there is little consistency or replication across models. Three studies each reported variable findings regarding the associations of alcohol misuse and of gender with *opioid misuse*. Only single studies have evaluated specific factors and OUD or high-risk obtainment of prescription opioids among older adults. The *OUD* study reported strong associations with a history of anxiety, pain interference (a measure of pain severity), and both marijuana and alcohol use. Older age, college education, and a prior history of opioid misuse were each found to be associated with *high-risk obtainment of prescription opioids* (in one study).

Research Needs on Predictors of Opioid-Related Disorders

While several studies have evaluated the relationships between factors and opioid misuse in older adults, additional research is needed to confirm (or refute) the observed associations. To improve confidence and increase the strength of the evidence base, additional studies that include factors in common (i.e., analyzed by previously published studies) should be considered. In particular, research is needed to determine the risk of *de novo* (incident) opioid-related disorders among older adults, and what factors may predict new opioid misuse or OUD. More work should also focus on distinguishing opioid dependence from OUD in various data sources, and how changes in definitions and assessment methods over time have impacted the findings of research studies. When examining such questions, consideration must be given to the temporality and type of opioid use. For example, studies examining the relationship between OUD and risk of opioid overdose death would likely focus on prevalent opioid use, while studies examining the transition from initial opioid use to long-term use to OUD would likely focus on new use of opioids and follow individuals longitudinally over time. These decisions regarding opioid use definitions and study design merit consideration in future work to maximize the ability of studies to address research needs.

Furthermore, there is a need to develop and validate accurate measures of opioid misuse among older adults. Studies have used multiple concurrent or proximal dispensing of opioid medications (drawn from claims data) as a measure of opioid misuse, but research validating such measures was not identified, and questions remain about the appropriateness of such measures. Provider factors, such as poor communication and coordination, could be an equally plausible explanation for the presence of multiple opioid prescriptions or dispensing in an older adults' drug claims. The use of multiple prescribers and pharmacies as a proxy for opioid misuse was also common, especially in large administrative database studies. Research should explicitly focus on the performance characteristics of various measures combining number of days of overlap between opioid prescriptions, number of different opioid prescribers, and number of different opioid dispensing pharmacies. If many such measures are, in fact, not a good proxy for opioid misuse (e.g., because these are actually palliative care patients appropriately using opioids), then much of the limited evidence base on factors associated with opioid misuse in older adults is unlikely to be provide information useful for identifying actual opioid misuse.

In addition, more research is necessary to understand the role of stress, anxiety, depression, trauma, and other behavioral and mental health conditions in increasing the risks of opioid

misuse and development of OUD. If these conditions are associated with opioid misuse and OUD among older adults, stress, mental health conditions, and behavioral conditions may serve as key predictors to intervene on.

Table 7. Heat map of multivariable analyses of associations between demographic and health status factors and opioid-related disorders*

Outcome	Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Age	Gender	Race	Comorbidity	ADL	QoL	Mental Health
Opioid use disorder	Choi 2017 28699829[91] Cross-sectional survey (general population)	Opioid use disorder NR (≥50 years)	▽ (Older)	NS	↑ Hispanic	NS			⬆ Anxiety
Opioid misuse	Carter 2019 30863796[90] † Cross-sectional registry (opioid-related ED visit)	Opioid misuse NR (≥65 years)	⬇ (Older)	↑ Female		△ Chronic conditions			
	Cochran 2017 28489491[92] Cross-sectional survey (general population)	Prescription Opioid Misuse Index NR (≥65 years) ‡		NS		NS			NS
	Park 2010 20664342[95] Cross-sectional survey (general population)	Opioid misuse 73 years (65-90)	NS	NS	NS		▽ (Better ADL)		△ Depression
High-risk behaviors	Gold 2016 27564407[93] Cross-sectional survey (general population)	High-risk obtainment of prescription opioids NR (≥60 years)	⬆ Older	↑ Female				NS	

Note: The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article (or outcome) and the strength and direction of the association, as described in Table 2. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., people in older age categories were at increased risk of high-risk obtainment of prescription opioids). Downward arrows are accompanied by text (in parentheses) that indicates the factor that is at decreased risk for the outcome, in keeping with the direction of the arrow (e.g., people in older age categories were at decreased risk of opioid use disorder).

Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. This heat map is organized by type of outcome (reason for hospitalization, reason for ED visit). Studies are presented in alphabetical order within outcome categories.

Abbreviations: ADL = activities of daily living, ED = emergency department, PMID = PubMed identifier, QoL = quality of life.

* 1 study that evaluated opioid misuse did not evaluate the factors in this table: Hoffman 2017 (PMID 28531306).
† Described as a cross-sectional study, but includes death as an analyzed outcome.
‡ In reported subgroup analysis.

Table 8. Heat map of multivariable analyses of associations between socioeconomic and related factors and opioid-related disorders*

Outcome	Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Income	Employment	Education	Rural	Social	Insurance
Opioid use disorder	Choi 2017 28699829[91] Cross-sectional survey (general population)	Opioid use disorder NR (≥50 years)		↑ Unemployed	NS		NS	
Opioid misuse	Carter 2019 30863796[90] Cross-sectional registry † (opioid-related ED visit)	Opioid misuse NR (≥65 years)	↑ Poorer			NS		↑ Medicaid Medicare ‡
	Cochran 2017 28489491[92] Cross-sectional survey (general population)	Prescription Opioid Misuse Index NR (≥65 years) ‡			NS	NS		
	Park 2010 20664342[95] Cross-sectional survey (general population)	Opioid misuse 73 years (65-90)					NS	
High-risk behaviors	Gold 2016 27564407[93] Cross-sectional survey (general population)	High-risk obtainment of prescription opioids NR (≥60 years)			⬇ (No college)		▽ (Connectedness)	

Note: See Table 2 for description of association coding and Table 7 for additional legend information.

Abbreviations: NS = not statistically significant, PMID = PubMed identifier.

* 1 study that evaluated opioid misuse did not evaluate the factors in this table: Hoffman 2017 (PMID 28531306).
† Described as a cross-sectional study, but includes death as an analyzed outcome.
‡ Primary payer (Medicaid at increased risk compared with Medicare, which in turn was at increased compared with neither Medicare nor Medicaid).

Table 9. Heat map of multivariable analyses of associations between pain and substance use disorder factors and opioid-related disorders

Outcome	Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Pain Cause	Pain Severity	Opioid Duration	Opioid Misuse	Substance Misuse	Tobacco
Opioid use disorder	Choi 2017 28699829[91] Cross-sectional survey (general population)	Opioid use disorder NR (≥50 years)	NS	⬆ Interference			⬆ Marijuana Alcohol	↑ Use
Opioid misuse	Carter 2019 30863796[90] Cross-sectional registry* (opioid-related ED visit)	Opioid misuse NR (≥65 years)	⬆ Injury				⬆ Alcohol	
	Cochran 2017 28489491[92] Cross-sectional survey (general population)	Prescription Opioid Misuse Index NR (≥65 years) †		NS		△ Misuse	NS (alcohol)	
	Hoffman 2017 28531306[94] Longitudinal retrospective (polyneuropathy)	Opioid abuse 68 years (NR)			NS			
		Opioid dependence (per ICD codes, not further defined) 68 years (NR)			⬆ ≥90 days			
	Park 2010 20664342[95] Cross-sectional survey (general population)	Opioid misuse 73 years (65-90)	NS	△ Severity			△ Alcohol	
High-risk behaviors	Gold 2016 27564407[93] Cross-sectional survey (general population)	High-risk obtainment of prescription opioids NR (≥60 years)				⬆ Misuse		NS

Note: See Table 2 for description of association coding and Table 7 for additional legend information.

Abbreviations: NS = not statistically significant, PMID = PubMed identifier.

* Described as a cross-sectional study, but includes death as an analyzed outcome.
† In reported subgroup analysis.

Factors Associated With Multiple Opioid Prescribers

Evidence Base

Only two studies reported a multivariable model of factors associated with having multiple opioid prescribers in older adults (Table 10).[96, 97] The models evaluated a variety of factors related to demographics, patient health status, socioeconomic and related factors, insurance status, pharmaceutical treatments, and substance use/misuse. While having multiple opioid prescribers is not in itself an indication of opioid misuse, it might reflect a high-risk patient behavior of intentionally seeking out multiple providers to procure more than recommended prescriptions (i.e., "doctor shopping"). It also might indicate fragmented or uncoordinated, and thus high-risk, patient care.[98-101] In the general population of all adults, multiple opioid pharmacies has been strongly associated with opioid abuse,[102] which raises the concern that it may also be associated with opioid misuse among older adults.

The two models largely overlapped in their evaluated factors; however, consistency varied both across and within models. Both models evaluated **age** and found that among older adults, the younger individuals (i.e., 65 to 74 and 75 to 84 years of age compared to ≥85 years;[96] each age decile compared to ages 66 to 70 years[97]) were at increased risk of using multiple prescribers (or as shown in the table, that older age groups were at decreased risk), with either strong or weak associations. Similarly, both found that **insurance** coverage (lower copays, Medicare Advantage vs. traditional Medicare, and Medicare Part D benefit in addition to Veterans Affairs [VA] insurance only) was associated with increased risk, strongly for no copay versus full copay, weakly for Medicare Advantage versus other Medicare coverage.

One of the two studies found weak associations for **gender** and **race**, such that men and non-Hispanic Blacks were at increased risk; however, the other study did not find these associations to be statistically significant. The first study also found that **rural** residents were at decreased risk (weak association) with multiple prescribers, but the second study found the opposite (also weak association). Regarding **income**, one study found weak associations between various measures of higher income and increased risk of multiple prescribers; the second study reported seemingly contradictory findings that higher median income was associated with lower risk, but that increased percentage of households below the poverty level (a poorly defined variable) was also associated with lower risk.

Among the factors evaluated by a single study only, strong associations were found for **mental health** conditions (sleep disorder and psychiatric diagnoses, but not suicide or self-injury), other associations were found for **comorbidities** (Hierarchical Condition Category risk score), **health utilization** (number of days), and **substance misuse**. No statistical association was found for tobacco use.

Summary of Factors Associated With Multiple Opioid Prescribers

Two multivariable models have identified a number of potential factors associated with having multiple opioid prescribers among older adults. Both found that younger age (among older adults) and specific insurance coverage factors (lower copays, Medicare Advantage vs. traditional Medicare, and Medicare Part D benefit in addition to VA only) were associated with having multiple prescribers. Other variables were inconsistently associated with having multiple opioid prescribers or were only evaluated by one model.

Research Needs on Predictors of Multiple Opioid Prescribers

As will be described in the section *Factors Associated with Hospitalizations or ED Visits*, below, a single study in older adults has found a strong association between the number of opioid prescribers and an increased risk of opioid-related hospitalizations. However, additional studies are needed to establish whether having multiple opioid prescribers is associated with harms. Regardless of whether this association may be due to harms caused by lack of coordination among prescribers or to high-risk patient behaviors (such as doctor shopping), determining the predictors that are associated with having multiple opioid prescribers would be of value. However, since only two studies are available, and they report some inconsistencies in findings, additional research is necessary to identify the predictors (or risk factors) for having multiple opioid prescribers in older adults. Additional studies should aim to include the factors examined by the prior two studies, in addition to other putative predictors, and assess the consistency of reported associations.

Furthermore, polypharmacy, not just coprescribing, deserves additional focus. Understanding the relationship between the number of medications an older adult is taking and subsequent opioid-related hospitalizations and ED visits would be a reasonable next step. Subdividing polypharmacy into potentially appropriate and inappropriate subtypes would then offer additional information valuable information. Medication appropriateness criteria like the Beers List might play a role in this future research.[103] Employing alternative measures of drug burden such as the Drug Burden Index, cumulative anticholinergic burden, and number of medications with sedative-hypnotic properties could also be valuable.[104]

Table 10. Heat map of multivariable analyses of associations between factors and multiple opioid prescribers

Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Age	Gender	Race	Comorbidity	HC Util	Mental Health	Income	Rural	Insurance	Nonop Pain Tx	Nonpain Tx	Substance Misuse	Tobacco
Jena 2014 24553363[96] Longitudinal retrospective (general population)	Multiple prescribers 69 (NR, Medicare)	↓ (Older)	↓ (Female)	↑ Non-Hispanic Black				↓ (*Poorer*)	↓ (Rural)	↑ MC Advantage	↑ Non-narcotic	↑ Various		
Suda 2017 28408172[97] Longitudinal retrospective (general population)	Multiple prescribers 78 years (≥66)	⬇ (Older)	NS	NS	△ HCC	△ Days of care	⬆ Sleep d/o Psych Dx	△▽ Variable *	↑ Rural	⬆ Smaller copay			↑ Abuse	NS

Note: The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article (or outcome) and the strength and direction of the association, as described in Table 2. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., non-Hispanic Blacks are at increased risk of having multiple prescribers). Downward arrows are accompanied by text (in parentheses) that indicates the factor that is at decreased risk for the outcome, in keeping with the direction of the arrow (e.g., people in older age categories at decreased risk of having multiple prescribers).

Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. Studies are presented in alphabetical order.

Abbreviations: HC Util = healthcare utilization, HCC = Hierarchical Condition Category risk score, MC = Medicare, Nonop Pain Tx = nonopioid pain treatment (use of), Nonpain Tx = nonpain treatment (use of), PMID = PubMed identifier, Psych Dx = psychiatric diagnosis, Sleep d/o = sleep disorder.

* Conflicting signals within regression (median income vs. percent below poverty level).

Factors Associated With Opioid-Related Harms (Octagon R3)

Four sets of studies have evaluated factors associated with opioid-related harms (Octagon R3 in Figure 1: Conceptual Framework):

1. Mental or physical health harms (Table 11)
2. Hospitalizations or ED visits (Table 12)
3. Opioid overdose (Table 13)
4. Death (Table 14)

Factors Associated With Mental Health or Physical Health Harms

Evidence Base

Four studies reported eight multivariable models of associations between opioid-related factors and mental or physical health outcomes (harms) (Table 11).[94, 105-107] The models analyzed six mental health outcomes, including depression, suicidal ideation, and substance misuse (alcohol or nonalcohol, nonopioid substance misuse), and two physical health outcomes (hip fracture and respiratory exacerbation). The models evaluated the association between these factors and opioid use, opioid use duration, opioid type, and opioid misuse.

Given that each study reported a different outcome (or set of outcomes), there is a lack of replication of findings across studies. Across studies (and outcomes), there were disparate associations related to **opioid use**. There was a strong association between status as an opioid user and risk of hip fracture in one study, but a weak association that new opioid users were at *decreased* risk of respiratory exacerbations compared with nonusers. However, this study (Vozoris 2016,[107]) found strong associations between new opioid use and chronic obstructive pulmonary disease (COPD) or pneumonia-related death, and weak associations with COPD or pneumonia-related ED visits and all-cause mortality (see sections *Factors Associated With Hospitalizations or ED Visits* and *Factors Associated With Death*). The third study that evaluated opioid use found no statistically significant association between past-year opioid use (without misuse) and suicidal ideation.

Opioid use duration was evaluated by two studies across six outcomes. Longer duration of opioid use was strongly associated with increased risk of hip fracture and weakly associated with depression and other substance (nonalcohol, nonopioid) dependence, but not "alcohol abuse," other "substance abuse," or other substance overdose.

Opioid type and opioid misuse were each evaluated by a single study. **Opioid type** (buprenorphine and, separately, strong opioids) was found to be strongly associated with increased risk of hip fracture. **Opioid misuse** was found to be weakly associated with increased risk of suicidal ideation.

Summary of Factors Associated With Mental Health or Physical Health Harms

Multivariable models have identified various measures of opioid use and misuse as potential factors associated with mental and physical health harms, but given the heterogeneity of analyzed outcomes and the sparseness of evaluated associations, no given association has been replicated.

Table 11. Heat map of multivariable analyses of opioid-related factors and opioid-related harms

Outcome	Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Opioid Use	Opioid Duration	Opioid Type	Opioid Misuse
Mental health	Hoffman 2017 28531306[94] Longitudinal retrospective (polyneuropathy)	Depression 68 years (NR)		↑ Long-term use		
		Alcohol abuse		NS		
		Other substance dependence		↑ Long-term use		
		Other substance abuse		NS		
		Other substance overdose		NS		
	Schepis 2019 30328160[105] Cross-sectional survey (general population)	Suicidal ideation NR (≥50 years)	NS			↑ Misuse
Physical health	Taipale 2019 30325873[106] Cross-sectional registry (Alzheimer disease)	Hip fracture 83 years (NR)	⬆ Use	⬆ Long-term use	⬆ Buprenorphine Strong opioid	
	Vozoris 2016 27418553[107] Longitudinal retrospective (COPD)	Respiratory exacerbation 77 years (≥66)	↓ (New use)			

Note: The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article (or outcome) and the strength and direction of the association, as described in Table 2. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., those with long-term opioid use were at increased risk of depression). Downward arrows are accompanied by text (in parentheses) that indicates the factor that is at *decreased* risk for the outcome, in keeping with the direction of the arrow (e.g., new opioid users were at *decreased* risk of respiratory exacerbation compared to no opioid use).

Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. This heat map is organized by type of outcome (mental and physical health harms). Studies (and outcomes) are presented in alphabetical order within outcome category.

Abbreviations: COPD = chronic obstructive pulmonary disease, PMID = PubMed identifier.

Research Needs on Predictors of Mental Health or Physical Health Harms

Few studies have evaluated the factors predicting mental or physical health harms associated with opioids specifically in older adults, and those that did each evaluated a unique set of outcomes. Additional studies are needed that focus on replication or better establish associations and replicate observed associations.

Furthermore, additional research is necessary on the relationships between isolation, psychiatric or mental health conditions, and caregiver support (lack thereof) and opioid-related harms. Efforts to link measures of isolation and caregiver support to medication data, or to employ existing datasets that have already combined this information, may be an effective way to generate more empirical evidence.

Factors Associated With Hospitalizations or ED Visits

Evidence Base

Five studies reported 11 multivariable models of opioid use-related factors associated with hospitalization and ED visits in older adults (Table 12).[96, 107-110] The models analyzed outcomes pertaining to all-cause hospitalization, opioid-related hospitalization, nonopioid-specific hospitalization, all-cause ED visit, and nonopioid-specific ED visit. The models evaluated factors associated with number of prescribers and opioid use, type, and misuse.

Outcomes varied across studies. Two studies evaluated all-cause hospitalization and, separately, all-cause ED visits, but they evaluated different types of factors (opioid use and opioid type). Another two studies evaluated three different nonopioid-specific hospitalization outcomes (pulmonary-related hospitalization and intensive care admission, and postsurgical hospital readmission). Each of the other outcomes was evaluated by a single study.

The most commonly evaluated factor category was **opioid use** (8 analyses/outcomes in 3 studies), although it was variably defined (new opioid use; history of opioid use, not misuse; frequency of preoperative opioid use; opioids "on hand" at surgery admission; and opioids prescribed postoperatively). Most analyses found associations between opioid use and risk of hospitalization or ED visit. One study found no statistically significant association with COPD or pneumonia-related hospitalizations or intensive care unit admissions.

No other factor category was analyzed by more than a single study. One study found that **opioid type** (schedule II opioids, see Table 12 abbreviation list) was weakly associated with increased risk of all-cause hospitalization and ED visits. One study found that **opioid misuse** was strongly associated with all-cause hospitalization and ED visits, but not statistically significantly associated with number of nights in the hospital or number of ED visits. One study found that increased **number of opioid prescribers** was strongly associated with increased risk of opioid-related hospitalizations.

Summary of Factors Associated With Hospitalizations or ED Visits

Five studies have reported multivariable analyses of opioid-related factors associated with hospitalization or ED visits among older adults with no replication of analyses. Overall, there is an indication that **opioid use**, **opioid type**, **opioid misuse**, and the **number of opioid prescribers** are all associated with increased risks of hospitalization and ED visits, but no specific analysis (between a given factor category and outcome category) was evaluated by more than one study.

Table 12. Heat map of multivariable analyses of factors associated with hospitalization or emergency department visits

Outcome	Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Opioid Use	Opioid Type	Opioid Misuse	No. Prescribers
All-cause hospitalization	Choi 2019 30585135[109] Cross-sectional survey and registry (general population)	All-cause hospitalization NR (≥50 years)	⬆ Use		⬆ Misuse	
		Number of nights in the hospital	↑ Use		NS	
	Kuo 2016 26522794[108] Longitudinal retrospective (without cancer)	All-cause hospitalization NR (≥66)		↑ Schedule II		
Opioid-related hospitalization	Jena 2014 24553363[96] Longitudinal retrospective (general population)	Opioid-related hospitalization 69 (NR, Medicare)				⬆ More prescribers
Nonopioid-specific hospitalization	Vozoris 2016 27418553[107] Longitudinal retrospective (COPD)	COPD or pneumonia-related hospitalization 77 years (≥66)	NS			
		ICU admission during COPD or pneumonia-related hospitalization	NS			
	Dasinger 2019 30879796[110] Longitudinal retrospective (surgery)	Postsurgical 30-day readmission 64 years (NR)	↑ Use			
All-cause ED visit	Choi 2019 30585135[109] Cross-sectional survey and registry (general population)	All-cause ED visit NR (≥50 years)	⬆ Use		⬆ Misuse	
		Number of ED visits	↑ Use		NS	
	Kuo 2016 26522794[108] Longitudinal retrospective (without cancer)	All-cause ED visit NR (≥66, Medicare)		↑ Schedule II		
Nonopioid-specific ED visit	Vozoris 2016 27418553[107] Longitudinal retrospective (COPD)	COPD- or pneumonia-related ED visit 77 years (≥66)	↑ New use			

Note: The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article (or outcome) and the strength and direction of the association, as described in Table 2. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., opioid users were at increased risk of all-cause hospitalization).

Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. This heat map is organized by type of outcome (reason for hospitalization, reason for ED visit). Studies (and outcomes) are presented in alphabetical order within outcome categories.

Abbreviations: COPD = chronic obstructive pulmonary disease, ED = Emergency Department, ICU = Intensive Care Unit, PMID = PubMed identifier, Schedule II = opioid with a high potential for abuse, per the Drug Enforcement Agency.

Research Needs on Predictors of Hospitalizations or ED Visits

Each of the identified studies evaluated different combinations of factors and outcomes. Thus, additional studies are needed that focus on replication or better establish or reproduce observed associations.

Factors Associated With Opioid Overdose

Evidence Base

Three studies reported multivariable models of factors associated with opioid overdose in older adults (Table 13).[94,111,112] The models each evaluated a unique set of factors related to demographics, patient health status, opioid factors, and substance use/misuse.

One study, Lo-Ciganic 2019,[112] reported a unique analysis of a machine-learning algorithm, which produced a "prediction score" for 268 "predictor" candidates. They report the 50 predictors with the highest prediction scores. However, they do not report association estimates that are comparable to other studies. Upon reviewing their bar graph of the 50 highest predictor scores, we noted that six predictors had scores of 0.6 or higher and the rest had scores <0.4. We, thus, categorized the top scores as strong associations. These included **age** (direction not reported), **comorbidities** (disability status), **opioid amount** (separately, average and total mean morphine equivalents and number of opioid fills), and **substance misuse** (combined substance or alcohol use disorder). Of note, several of the factors analyzed were area-level measures (e.g., percentage of unemployment in the participant's area of residence). Interpretation of these factors are subject to ecological fallacy (where a spurious association is made about an individual based on aggregate data for a group). However, the six highest predictor scores were measured at the level of the individual participant.

We did not extract or tabulate the other 44 reported predictors; however, these included: **race** (not defined), other **comorbidities** (falls, fractures, and other injuries; area-level percentage of poor to fair health), **mental health** (mood disorders, anxiety disorders, psychoses), low **income** (low-income subsidy, area-level percentage of children in poverty), area-level percentage of **unemployment**, **insurance** status (area level penetration of Medicare Advantage, area level percentage of women in fee-for-service Medicare), **opioid type** (not defined; duration of short-acting opioid use, duration of long-acting opioid use), **nonpain treatments** (antidepressants), **opioid misuse** (days from last overdose event), other **substance misuse** (early refills, area-level percentage of excessive drinking, drug use disorders), and **benzodiazepine** use (and days of concurrent opioid and benzodiazepine use).

Also of note, as implied above, many of the predictors were poorly defined, such as **age** (for which no direction of association was indicated), **type of opioid**, and **race** (for which there was no indication of which category was at increased risk).

The second study reported only that **long-term opioid use** was strongly associated with opioid overdose. The third study found that **opioid misuse** (supplied opioids exceeded daily prescription) and increased **numbers of prescribers** or, separately, pharmacies were both strongly associated with opioid overdose.

Table 13. Heat map of multivariable analyses of associations between factors and opioid overdose

Study PMID Design (Specific Population)	Outcome (Per Study) Mean or Median Age (Range)	Age	Comorbidity	Opioid Duration	Opioid Amount	Opioid Misuse	Substance Misuse	No. Prescribers
Carey 2018 29800019[111] Longitudinal retrospective (general population)	Opioid overdose NR (NR, Medicare)					⬆ Misuse		⬆ More prescribers More pharmacies
Hoffman 2017 28531306[94] Longitudinal retrospective (polyneuropathy)	Opioid overdose 68 years (NR)			⬆ Long-term use				
Lo-Ciganic 2019* 30901048[112] Longitudinal retrospective (general population)	Opioid overdose 68 years (NR, Medicare)	ND † ‡	⬆ ‡ Disability status		⬆ ‡ MME Opioid fills		⬆ ‡ Substance or alcohol	

Note: The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article and the strength and direction of the association, as described in Table 2. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., those with comorbidities are at increased risk of opioid overdose).

Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. Studies are presented in alphabetical order.

Abbreviations: MME = mean morphine equivalents, ND = no data reported, PMID = PubMed identifier.

* In total, 50 "predictors" are ranked; only those with the highest prediction scores are reported here. Several ranked predictor (not among those with the highest scores) were based on regional measures (e.g., "area level percentage of unemployment"), which are subject to ecological fallacy.
† The study does not indicate the directionality of the association.
‡ Among the most important predictors ("importance factor" >40%).

Summary of Factors Associated With Opioid Overdose

Three studies evaluated factors associated with opioid overdose in older adults. One study ranked numerous (often poorly defined) factors by strength of association; the other two evaluated nonoverlapping sets of factors. Nevertheless, one study each reported strong associations for opioid overdose among older adults with **age** (however, the direction of the association was not reported), **disability status**, **opioid use duration**, **amount of opioids used**, **opioid misuse**, **other substance misuse**, and **number of opioid prescribers**.

Research Needs on Predictors of Opioid Overdose

Most results are from various machine learning algorithms reported by one large study, so a need likely exists for researchers to replicate the findings of this study through the use of parametric statistical regression models. This will require at least one or more confirmatory studies.

Factors Associated With Death

Evidence Base

Five studies reported nine multivariable models of factors associated with opioid-related mortality or opioid-related factors associated with nonopioid-related deaths in older adults (Table 14).[90,107,113-115] The models analyzed all-cause death; opioid-related death; nonopioid-specific death, including COPD- or pneumonia-related death; and drug overdose death (any drug). The models evaluated factors related to demographics; opioid use, misuse, and prescription; socioeconomic and related factors; clinician factors; and other substance use. Of note, two of the studies were conducted based on measures (of factors and outcomes) at the county or state level (as opposed to at the individual participant level). Both Grigoras 2018 and Zoorob 2018 evaluated death rates in counties (or states) and rates or percentages of people in a given category (e.g., White race) within the same counties (or states). These analyses are subject to ecological fallacy (where a spurious association is made about an individual based on aggregate data for a group).

Across outcomes, no factor category was reported on by more than two studies. **Race** and **income** were each examined by two studies (but as percentages of people in a race/ethnicity category or who were in poverty), both of which found associations between these factors and rates of death. The two studies reported models for five separate outcomes, and both found that higher percentages of people who were White (or non-Black/non-Hispanic) in a given area were associated with higher death rates. The same two studies reported that higher poverty rates were also associated with increased rates of death.

Three studies (reporting on three outcomes) evaluated different aspects of **opioid use**. Two studies found associations between opioid use (either new use—weak association—or tramadol use specifically—strong association) and all-cause death. One of these studies also found that new users of opioids were (strongly) at increased risk of COPD or pneumonia-related death. Another study found a statistically significant association between the percentage of opioid users among older adults in a county and drug-overdose death rate.

Single studies identified the following factors as being associated with higher risk of death: lower level of **education** (more residents without a high school diploma in a given area), ***not* rural** residency, **specialty** of the opioid prescriber (various, including emergency medicine), and rate of **benzodiazepine** use in a given area. Possibly counterintuitively, one study found that history of **opioid misuse** was associated with *lower* odds of patient encounters ending in death

versus routine discharge. Only the association between tramadol use and risk of COPD or pneumonia-related death could be classified as a strong association.

Table 14. Heat map of multivariable analyses of opioid-related associations between factors and death

Outcome	Study PMID	Outcome (Per Study) Mean or Median Age (Range)	Race	Income	Education	Rural	Specialty	Opioid Rx Rate	Opioid Use	Opioid Misuse	Benzo
All-cause death	Carter 2019 30863796[90] Cross-sectional registry* (opioid-related ED visit)	Death (in ED) NR (≥65 years)								↓ (Misuse)	
	Vozoris 2016 27418553[107] Longitudinal retrospective (COPD)	All-cause death 77 years (≥66)							↑ New use		
	Zeng 2019 30860559[114] Longitudinal retrospective (no prior cancer)	All-cause death 70 years (≥50)							⬆ Tramadol vs. NSAID		
Opioid-related death	Grigoras 2018 29159797[113] Cross-sectional registry† (general population) ‡	*Opioid-related death rate NR (NR, Medicare)*	◿ *% White* ‡	◿ *% Poverty* ‡			◿ *Various*	◿ *Higher rate* ‡			
		Synthetic opioid-related death rate	◿ *% White* ‡	◿ *% Poverty* ‡				◿ *Higher rate* ‡			
		Natural and semisynthetic opioid-related death rate	◿ *% White* ‡	◿ *% Poverty* ‡				◿ *Higher rate* ‡			
		Methadone-related death rate	◿ *% White* ‡	◿ *% Poverty* ‡				◿ *Higher rate* ‡			
Nonopioid related death	Vozoris 2016 27418553[107] Longitudinal retrospective (COPD)	COPD or pneumonia-related death 77 years (≥66)							⬆ New use		
	Zoorob 2018 29537112[115] Cross-sectional registry† (general population) ‡	Drug overdose death rate NR (NR, Medicare)	△ % Non-Black/ Hispanic ‡	△ % Poverty ‡	△ % <HS ‡	↓ (Rural)			△ Higher use rate ‡		△ Benzo use rate ‡

Note: The heat map lays out each analyzed outcome within each article across rows. The colors and arrows indicate which factor categories were reported in each article (or outcome) and the strength and direction of the association, as described in Table 2. Direction of the arrows indicates the direction of the association. Accompanying text within the cells indicates the factor that is at increased risk (e.g., Whites were at increased risk of death). Downward arrows are accompanied by text (in parentheses) that indicates the factor that is at decreased risk for the outcome (e.g., rural residents were at decreased risk of drug overdose death).

Across heat map tables, the columns are presented in the same order: demographics, markers of health status, socioeconomic and related factors, pain cause and severity, healthcare specialist, opioid factors, other medication factors, opioid misuse, other substance use/misuse, and opioid stewardship. This heat map is organized by type of outcome (cause of death). Studies are presented in alphabetical order within outcome categories.

Abbreviations: <HS = less than a high school education; Benzo = benzodiazepine use, COPD = chronic obstructive pulmonary disease, ED = emergency department, HS = high school education, NSAID = nonsteroidal anti-inflammatory drug, Op Rx Rate = rate of opioid prescribing, PMID = PubMed identifier, Specialty = prescriber specialty.

* Described as a cross-sectional study but includes death as an analyzed outcome.
† Crossed with a death registry.
‡ All variables (factors and outcomes) are based on county-level (or state-level) rates (or percentages). Thus, the whole analysis is subject to ecological fallacy.

Summary of Factors Associated With Death

Across five studies, multivariable models have identified a number of potential factors associated with death related to opioid use (or among older adults using opioids). Associations have been replicated only for **race**, **income**, and **opioid use**, but only by two studies each and the studies of opioid use evaluated different opioids. However, these factors applied to communities at high risk, not necessarily to individuals. Two factors have been found to be strongly associated with death (**new opioid use** and **tramadol** prescription), but each by only a single study and for different outcomes (all-cause death and nonopioid related death, respectively).

Research Needs on Predictors of Death

Since the associations between most factors and death have been evaluated by only a single study, additional studies are needed to determine likely candidates as predictors of death pertaining to opioid use in older adults. In particular, studies employing a specific and, if possible, validated definition of opioid-related death are needed.

Additional Research Needs and Gaps Pertaining to Predictors

Based on discussions with Key Informants and within the research team, we identified a number of research needs that are not addressed by published multivariable risk factor analyses or that do not cleanly fit within Octagons R2 or R3 in the Conceptual Framework. These are discussed in roughly the temporal order that people interact with opioid use, starting with patient demographics.

Research Needs About the Definition of "Older Adult"

Future research should consider whether it is appropriate to identify individuals aged 50 to 60 or 50 to 65 as "older." If that term is applied to individuals younger than 60 or 65 years of age, researchers should consider providing a clear justification or rationale (e.g., biological aging) for the application of one age threshold versus another. Research into the impact of varying the age threshold used to define adults as "older" might be warranted for many of the questions related to opioid use, misuse, and OUD in older adults. The rationale is that intergenerational or birth cohort differences could result in qualitatively different inferences depending on the age groups chosen for a given study. Individuals currently aged 50 to 65 years (Baby Boomers II and Generation X) are likely to have different predictors of opioid-related harms compared to individuals aged 65 and older (Baby Boomers I), in part due to differences in age and comorbidities, but in part due to different life and cultural experiences. Thus, an important gap in knowledge is what, if any, evidence on predictors of opioid-related outcomes in younger adults

or overall populations spanning many age groups is generalizable to older adults. Similarly, individuals aged 85 or older (sometimes referred to as the "oldest old") may have unique predictors related to age-related physiological changes that are not present in younger subgroups of the older adult population. Complicating the issue of deciding who most appropriately could be grouped as being "older" is that socioeconomically disadvantaged individuals (and others with health care disparities) have higher rates of chronic diseases, functional limitations, and high-risk behaviors (such as smoking), along with poorer access to healthcare. Thus, they may physiologically age earlier than their more-advantaged peers.[116]

Research Needs About Birth Cohort, Age, and Substance Use

Research has not explicitly quantified the interaction or interplay between birth cohort, age, and nonopioid substance use (e.g., alcohol) as predictors of opioid misuse and OUD. The aging of the "baby boomer" cohort, along with the differing patterns of substance use and misuse among these individuals, might result in unique patterns of opioid misuse compared to the prior birth cohort (born in the early 1940s or before). In addition to nonopioid substance use and use disorders, baby boomers may have unique characteristics that result in an increased rate of opioid misuse, OUD, and overdose as they age into the older adult cohort over time. More research is necessary to distinguish between these potential age and birth cohort influences. Such research should also take into account temporal trends in other important factors that might influence opioid use and misuse, such as demographic changes, increased life expectancy, greater illicit drug availability, improved access to healthcare, and the development and implementation of harm reduction and substance use disorder treatment services.

In addition, more research is necessary to understand the differences that may exist between older adults with lifelong risk factors for substance use disorders and mental health conditions who develop OUD versus older adults who experience a stressful event later in life and develop OUD. Some forthcoming research may help to provide some evidence on these topics. American Institute for Research investigators have recently tested the use of the Current Opioid Misuse Measure (COMM) for use with people with disabilities caused by arthritis, severe spinal osteoporosis and spinal stenosis who use opioids to manage chronic pain. Preliminary results suggest that a subset of the COMM items is valid for assessing opioid misuse in this population.

Finally, the associations between age and opioid-related outcomes must be interpreted carefully in the absence of data and studies that have examined age-period-cohort associations. It is possible that age may operate as a proxy for historic experience (e.g., more opportunity to experience events like surgeries that require opioids) and trends (e.g., increasing numbers of prescriptions for opioids during some time periods). Age-period-cohort research is necessary to disentangle the associations between age, period, birth cohort, and opioid-related outcomes before any associations between age and opioid-related outcomes can be properly interpreted.

Summary of Evidence Base on Predictors Across Outcomes

This section repeats observations from preceding sections.

Most of the current evidence base regarding factors associated with opioid-related outcomes is sparse, particularly for definitive opioid-related harms. Table 1 summarized the evidence base for factor-outcome associations with at least three studies. (More detailed summaries of the evidence base for association studies are provided in Appendix D, Tables D-3, D-5, and D-6.) Most notable is that the bulk of such evidence relates to long-term opioid use, an outcome which

for some individuals might indicate high-risk behavior or even opioid misuse, but for many individuals may indicate appropriate treatment of chronic pain.

Summary of Factors Associated With Opioid Use (Octagon R1)

One set of studies has evaluated factors associated with opioid use (Octagon R1 in Figure 1: Conceptual Framework). The only outcome pertaining to opioid use among eligible studies was long-term opioid use. The largest set of studies evaluated this outcome. No study evaluated opioid use where benefits outweigh harms.

Overall, 22 multivariable models have evaluated a large number of potential factors associated with **long-term opioid use** among older adults. Table 1 highlights the findings for factor-outcome pair associations analyzed by at least three studies.

Studies were consistent (in full agreement) that—in nine studies—opioid use prior to surgery or injury (or early use after surgery) and—in nine studies—greater amounts of opioids (more prescriptions or higher dose) are the factors with mostly strong associations.

Other consistent associations, but with largely weak associations, were found with back pain (7 studies, 3 with strong associations), depression (11 studies, all weak associations), concomitant NSAID use (4 studies, all weak associations), and fibromyalgia (3 studies, all weak associations).

Studies were mostly consistent (≥75% agreement) that benzodiazepine use (6 of 7 studies, 3 with a strong associations), comorbidity scores (6 of 8 studies, 2 with strong associations), variably or undefined substance misuse (9 of 10 studies, 2 with strong associations), tobacco use (5 of 6 studies, 1 with a strong association), and low income (8 of 10 studies, all with weak associations) were associated with long-term opioid use.

Studies were also mostly consistent that alcohol "abuse" (4 of 5 studies) and healthcare utilization (3 of 4 studies) were *not* associated with long-term opioid use; however, one of these latter studies found a strong association between "any hospitalization" and long-term use.

Factors with variable findings of association (evaluated by at least 3 studies) included gender (8 of 18 studies found weak associations with female gender; 2 found associations with male gender, 1 strong), age among older adults (8 of 14 studies found mostly weak associations with younger age; 2 found weak associations with older age), Black race (8 of 12 found weak associations, but 5 associations were with increased and 3 were with decreased likelihoods), dementia (2 each, among 5 studies found associations with increased and with decreased likelihood), rural or non-urban residence (1 each, among 5 studies found associations with increased and with decreased likelihood), prescription of long-acting opioids (2 of 3 with studies found associations, both strong), unmarried relationship status (2 of 3 studies found associations, 1 strong), and use of muscle relaxants (2 of 3 studies found weak associations).

Summary of Factors Associated With Opioid Misuse and Related Outcomes (Octagon R2)

Two sets of studies have evaluated factors associated with opioid misuse (Octagon R2 in Figure 1: Conceptual Framework): opioid-related disorders and multiple opioid prescribers.

Six studies have evaluated factors associated with **opioid-related disorders** among older adults, including OUD, opioid misuse, and high-risk behaviors, but since the researchers largely analyzed different sets of factors, there is little consistency or replication across models. Three studies each reported variable findings regarding the associations of alcohol misuse and of gender with *opioid misuse*. Only single studies have evaluated specific factors and OUD or high-

risk obtainment of prescription opioids among older adults. The *OUD* study reported strong associations with a history of anxiety, pain interference (a measure of pain severity), and both marijuana and alcohol use. Older age, college education, and a prior history opioid misuse were each found to be associated with increased risk of *high-risk obtainment of prescription opioids* (in one study). Only two studies evaluated factors associated with having **multiple opioid prescribers** (potentially an indication of misuse or a risk factor for harms related to uncoordinated care). Both found that younger age (among older adults) and specific insurance coverage factors (lower copays, Medicare Advantage vs. traditional Medicare, and Medicare Part D benefit in addition to VA only) were associated with having multiple prescribers. Other variables were inconsistently associated with having multiple opioid prescribers or were only evaluated by one model.

Summary of Factors Associated With Opioid-Related Harms (Octagon R3)

Four sets of studies have evaluated factors associated with opioid-related harms (Octagon R3 in Figure1: the Conceptual Framework): mental or physical health harms, hospitalizations or ED visits, opioid overdose and death.

Few studies (two each) have evaluated opioid-related factors associated with **mental health** or **physical health harms** in older adults. A single study found that opioid use, duration of use, and opioid type are strongly associated with increased risk of hip fracture, but other studies found weak or no associations with outcomes. Each of the four studies evaluated different outcomes and no factor-outcome association was replicated. Additional research is needed.

Outcomes related to **hospitalizations** or **ED visits** have been evaluated in multivariable models in five studies. Strong associations were reported between opioid use or misuse and both all-cause hospitalization and ED visits, as well as between increased number of opioid prescribers and opioid-related hospitalizations. However, the five studies each evaluated different combinations of factor categories and outcome categories, such that no finding has been replicated. Additional research is needed.

Three studies evaluated factors associated with **opioid overdose** in older adults. One study ranked numerous (often unclearly defined) factors by strength of association; the other two evaluated nonoverlapping sets of factors. Nevertheless, one study each reported strong associations for opioid overdose among older adults with age, disability status, opioid use duration, amount of opioid use, opioid misuse, other substance misuse, and number of opioid prescribers. Additional research is needed.

Among five studies that have evaluated factors associated with **death** related to opioid use in older adults, two reported that counties with higher percentages of people who are White or in poverty are associated with higher risks of opioid-related or drug overdose deaths. Notably, these measures apply to communities, not necessarily individuals, at high risk. Other specific associations have each been evaluated by only a single study (including strong associations for new opioid use and tramadol prescription). Additional research is needed.

Interventions Related to Opioid Use in Older Adults

Overview of Literature

We identified 16 studies (in 17 articles) that address interventions to appropriately reduce opioid prescriptions, reduce harms, identify misuse, or treat misuse in older adults. A summary of the identified intervention studies is presented in Table 15.[117-133] The descriptions are organized by topic (or purpose) of the interventions, by level of the intervention (screening,

patient, clinician, and healthcare system), then by study. Appendix D Tables D-4 to D-6 include further details of each study.

Only two were randomized controlled trials. In both trials clinicians, not patients, were randomized.[119,122] Most studies were secondary database or registry analyses (e.g., among Medicare Part D enrollees) or cross-sectional survey studies. Five studies were pre-post studies (with data collected and compared before and after an intervention was introduced). Two studies were conducted specifically among caregivers, in one study as a focus group and in the other for training of motivational interviewing. Further descriptions are provided below.

Nine of the studies evaluated interventions to reduce opioid prescriptions or use, which align with Triangle I1 in the Conceptual Framework (Figure 1), and primarily address the stage at which decisions are being made about which treatment(s) to use (Conceptual Framework Rectangle C). One of these interventions also was designed to minimize patient activities that may lead to opioid misuse (Triangle I2). Six additional studies evaluated screening tools to identify people at increased risk of opioid-related disorders (also Triangle I2). Two studies evaluated clinician-level interventions to reduce harms related to opioid use or misuse in older adults (Rectangle F and Triangle I3 in the Conceptual Framework). Few studies evaluated patients' pain. No studies addressed safe prescription practices among older adults appropriately using opioids (Rectangle D) and no studies evaluated either management of opioid misuse in real (as opposed to hypothetical) older adults or treatments for OUD in older adults (Rectangle F).

There are numerous gaps in the evidence base related to the various stages depicted in the Conceptual Framework (Rectangles B to F) and the types of interventions (Triangles I1 to I3), not to mention issues related to applicability or heterogeneity of treatment effect suggested by the various potential predictors (or effect modifiers). Even where there is evidence, almost none of the intervention studies have been replicated.

Table 15. Studies that evaluate interventions of interest

Intervention Topic	Intervention Category	Study PMID	Intervention	Design	Sample Size	Result*
Reduce opioid prescriptions or use where harm outweighs benefit (Conceptual Framework Triangle I1)	Patient-level	Darchuk 2010 20735746[117]	Pain rehabilitation program	Single group, prospective	78	Improved
		Rose 2016† 26431852[118]	Patient education pamphlet†	NRCS, prospective	172	NS
	Clinician-level	Pasquale 2017† 29199396[119]	Provision of patient information; Educational materials	RCT (clinicians randomized)	2391	NS
		Gugelmann 2013 23906621[120]	Bundle of educational modalities	NRCS, prospective	2212	Improved
	Hospital system-level	Chen 2019 31314748[121]	Opioid Safety Initiative	NRCS, pre-post, retrospective	60,056	Improved
	Healthcare system-level	Vicentini 2019 31810456[122]	Free acetaminophen prescription	RCT (clinicians randomized)	117	NS
		Yarbrough 2018 28101955[123]	PDMP	NRCS, retrospective (registry)	6920	Improved
		Moyo 2017, 2019 28498498[124], 31372990[125]	PDMP	NRCS, retrospective (registry)	310,105	Improved
		Schaffer 2018 29581162[126]	Tamper-resistant oxycodone	NRCS, retrospective (registry)	5055	NS
Identify or reduce opioid-related disorders (Conceptual Framework Triangle I2)	Screening	Park 2011 21143370[127]	PMQ	Single group, prospective	150	Useful tool
		Tiet 2019 30947051[128]	SoDU	Single group, prospective	1283	Validated tool
		Beaudoin 2016 27426210[129]	PDUQp	Single group, retrospective	38	Validated tool
		Henderson 2015 26056833[130]	PDUQp	Single group, prospective	88	Validated tool
		Cheng 2019 31234786[131]	SDS	Single group, prospective	246	Validated tool
		Draper 2015 25247846[132]	ASSIST	Single group, retrospective	210	Unclear
	Clinician-level	Pasquale 2017† 29199396[119]	Provision of patient information; Educational materials	RCT (clinicians randomized)	2391	NS
	Patient-level	Rose 2016† 26431852[118]	Patient education pamphlet†	NRCS, prospective	172	Improved
Reduce opioid-related harms (Conceptual Framework Rectangle F and Triangle I3)	Clinician-level	Chang 2019 31187888[133]	Motivational interviewing training	Single group, prospective	31 students ‡	Possibly improved
		Pasquale 2017† 29199396[119]	Provision of patient information; Educational materials	RCT (clinicians randomized)	2391 §	NS

Abbreviations: ASSIST = Alcohol, Smoking and Substance Involvement Screening Test, AUDIT-C = Brief Alcohol Use Disorders Identification Test, NRCS = nonrandomized comparative study, PDMP = prescription drug monitoring programs, PDUQp = Prescription Drug Use Questionnaire, patient version, PMID = PubMed identifier, PMQ = Pain Medication Questionnaire, RCT = randomized controlled trial, SDS = Severity of Dependence Scale, SoDU = Screen of Drug Use.

* Qualitative assessment of effect of intervention, categorized as statistically nonsignificant (NS), Improved (statistically significant effect of intervention to reduce harm or to increase benefit), Worsened (statistically significant effect of intervention to increase harm or to decrease benefit), Mixed (benefit for some outcomes, harm for others).
† Note that this study is in the table multiple times.
‡ The older adults with opioid misuse were, in fact, hypothetical patients that the students used as case examples.
§ The clinicians' patients were, in fact, those who were predicted to be at increased risk for opioid abuse, not patients diagnosed with opioid misuse (or opioid use disorder).

Interventions To Reduce Opioid Prescribing for Older Adults for Whom Harms Outweigh Benefits (Triangle I1)

Evidence Base

We identified nine studies of interventions to reduce opioid prescribing or use in older adults (first set of subrows in Table 15). These studies align with Triangle I1 in the Conceptual Framework (Figure 1) at the stage where decisions are being made regarding treatment. Interventions were aimed at patients (rehabilitation and education), clinicians (providing information and education), hospital systems (an opioid safety initiative), and healthcare systems (free acetaminophen prescriptions, prescription drug monitoring programs (PDMP), and tamper-resistant opioids). Of note, among studies that had the goal of reducing overall opioid prescriptions or use, none specifically assessed "appropriate" reduction of opioid prescriptions or use (e.g., for patients whose risks of harms outweigh benefits). However, only four studies also evaluated effects of the interventions on pain (and/or mental health and quality of life) outcomes. Only the hospital systems-level study assessed reducing opioid prescriptions or use specifically in the context of maintaining adequate pain control

Training Patients

Two studies assessed training or education of patients with the goal of reducing opioid use (identified as "Patient-level" in Table 15).

Darchuk 2010[117] described the Mayo Clinic Comprehensive Pain Rehabilitation Center program, an **intensive 3-week, group-based, outpatient interdisciplinary pain rehabilitation program**. As described by the authors, the cognitive–behavioral model serves as the basis for treatment, which incorporates physical therapy, occupational therapy, biofeedback and relaxation training, stress management, wellness instruction (e.g., sleep hygiene, healthy diet), chemical health education, and pain management training (e.g., activity moderation, elimination of pain behaviors). The program's goals emphasize functional restoration and self-management of chronic pain symptoms. An important treatment goal for all patients in this program is the discontinuation of opioid and simple analgesics taken for relief of chronic pain. The study was conducted as a pre-post design, without a separate concurrent comparator group. The authors reported on an older adult subgroup comprising 78 individuals aged ≥60. The study found a large reduction in opioid use after discharge from the program, which occurred in parallel with reduced depression, catastrophizing, pain severity, and pain interference, and increased perceived control, and physical and social functioning.

Rose 2016[118] evaluated the effect of a **patient education pamphlet** on opioid use. The pre-post study was conducted in 172 patients who had received either a total knee or hip arthroplasty,

with a mean age of 63 years. The goal of the education was not specifically designed to reduce opioid use. The pamphlet covered educational domains about safe opioid storage, opioid weaning, and opioid disposal. However, the study also reported on postoperative opioid cessation, finding no difference in opioid cessation rates between groups. Furthermore, no differences were found in pain outcomes.

One systematic review is ongoing that, at least tangentially, will address issues related to **appropriate prescriptions**. The ongoing systematic review by Alvan et al.[134] is investigating risks and benefits of pharmacological treatment of older (≥65 years) patients with common pain conditions. They are also looking for qualitative research studies that assessed the experiences of older adults with pain. The review is expected to be published in 2020.

Clinician-Level Interventions (Information and Training)

Two studies assessed education of or providing information to clinicians with the goal of reducing opioid use (identified as "Clinician-level" in Table 15).

A cluster-randomized trial assessed the value of providing information to physicians about Medicare patients' opioid "abuse" risk. Pasquale 2017[119] used a regression model to predict that 2,391 patients enrolled in Medicare plans were at increased risk for opioid "abuse" and then linked the patients with their prescribing physicians (N=4,353). Those physicians were randomized to be sent either **"patient information," educational materials for diagnosis and management of pain, both patient information and educational materials, or there was no communication.** The study evaluated patients' opioid prescriptions, "chronic high-dose opioid use" (multiprescriber, multipharmacy, high-dose use ≥90 days), "uncoordinated opioid use" (multiprescriber), among other opioid-related outcomes. The study found that the interventions did not affect these outcomes, but they did not evaluate patient-level outcomes, including pain and functioning.

Gugelmann 2013[120] evaluated a **"bundle" of interdisciplinary educational modalities** provided to ED nurse practitioners with the specific goal of decreasing opioid discharge pack use in patients treated and released from the ED, particularly those at risk for dependence. These included: lectures, journal clubs, case discussions, and an electronic medical record decision support tool." In a larger evaluation of all ED patients, they report the results for a subgroup of 2212 individuals aged 65 years or older who were treated before (N=1360) or after (N=852) the training (interrupted pre-post design). The single result reported for this older adult subgroup related to prescription of oxycodone/acetaminophen "4-packs," with a statistically significant decrease in prescriptions during the postintervention period. The study did not report comparative pain outcomes for older adults. Of note, Gugelmann et al. was the only pertinent study related to opioid use found by a 2016 systematic review, by Maree et al.,[54] of opioid (and benzodiazepine) misuse in older adults.

Hospital System-Level Intervention

One study assessed implementation of an opioid reduction program in a hospital system (identified as "Hospital system-level" in Table 15).

The study, conducted in the VA Health Care System, evaluated rollout of an "**Opioid Safety Initiative**" nationwide. The initiative included training and education of physicians and "active support" of patients and physicians.[135] The initiative has a goal of reducing non-cancer pain opioid treatment to <200 morphine-equivalent mg daily, with active monitoring of patients with higher prescribed dosages. Chen 2019[121] compared patients undergoing total knee arthroscopy before and after rollout of the initiative (N=60,056). The study evaluated pain scores and opioid

and nonopioid prescriptions. The study found substantial decreases in chronic opioid use together with "minimal" impacts on pain scores (i.e., no worsening of pain, despite decreased opioid use).

Healthcare System-Level Interventions

Four studies evaluated the association of national or State-level systems changes and changes in opioid prescriptions (at a population level). None evaluated pain outcomes.

One trial randomized clinicians to being able to prescribe **acetaminophen at no charge** to their patients with knee osteoarthritis (as opposed to providing recommendations for over-the-counter acetaminophen). Among 117 patients (all ≥65 years, 32% using opioids prior to the trial), Vicentini 2019 found no difference in average daily opioid dose or number of opioid uses between groups.[122] The study did not report patient-centered outcomes such as pain or functioning.

Two studies evaluated **prescription drug monitoring programs (PDMP)** in the U.S. Yarbrough 2018[123] evaluated data on Medicare enrollees in all 50 states, comparing states with PDMPs that (1) allowed both prescribers and dispensers to have access to the program, (2) provided online access to the program, and (3) required reporting of all pharmacy prescriptions with states whose PDMPs did not meet these criteria. The number of opioid prescriptions were compared between states. The study concluded PDMPs had a modest effect on oxycodone use. Moyo 2017[124] and 2019[125] also evaluated data on Medicare enrollees (with data reported specifically for those ≥65 years), initially (in 2017) in 21 states that either did or did not have PDMPs, expanded nationwide (in the 2019 publication). The study reported opioid prescriptions at the state level, as measured by kilograms of opioids dispensed, number of dispensed prescriptions, and opioid dose per prescription. This study also found significant reductions in opioid prescriptions and daily doses associated with PDMP. Neither study evaluated whether the amounts of opioids prescribed were "appropriate" or adequate to manage pain.

The third study evaluated the effect of the introduction of a **tamper-resistant formulation** of oxycodone CR (controlled release) on opioid use in Australia. As part of a larger study of individuals prescribed controlled-release oxycodone, Schaffer 2018[126] evaluated 5,055 older adults ≥65 years. The study compared prescriptions for oxycodone CR specifically, changes to "strong" opioids, and switches to other opioids related to the change in formulation but found no significant association between oxycodone formulation and opioid use. No patient-level outcomes, including pain, were reported.

Research Needs Regarding Interventions To Reduce Opioid Prescribing for Older Adults for Whom Harms Outweigh Benefits (Triangle I1)

With the exception of PDMP, each of the interventions to reduce opioid use was evaluated by only a single study; thus, there is a need to replicate the findings and expand upon the research base. Furthermore, the studies all evaluated overall opioid use, instead of aiming to reduce opioid use where harms outweigh benefits. Future studies should attempt to better focus on minimizing "inappropriate" use. Such attempts might first require ethics research to define "appropriate reductions" in opioid use, as well as policy research to understand the unintended adverse consequences of policies that aim to reduce potentially inappropriate opioid use.

Research Needs Specific to Multidisciplinary Pain Treatment Teams

Significantly more research is needed on care models that organize multiple providers (e.g., geriatrics, pain medicine, mental health, behavioral health, pharmacy, nursing) into a pain

treatment team (e.g., as in interdisciplinary pain programs or clinics). While the ED intervention described in Gugelmann 2013[120] addressed the portion of the conceptual framework related to reducing suboptimal opioid prescribing, it did not involve any formal efforts to organize providers into a pain treatment team. Furthermore, no interventions appear to address how exactly to establish clear delineations of responsibility for pain management in a multidisciplinary pain team. Furthermore, Key Informants and others believe that interdisciplinary pain teams could or should include a pharmacist capable of performing a comprehensive geriatric medication evaluation, who would then either make recommendations to prescribers or function semi-autonomously under a collaborative practice agreement (i.e., protocol) to make modifications to an older adult's medication regimen. Studies of this potential care model would be highly valuable.

Research Needs Specific to Deprescribing Protocols and Sharing Responsibility

Related to care models that organize multiple providers, one of the most important areas for future research is understanding who is responsible for prescribing an opioid, monitoring its continued use, and deprescribing the opioid. Deprescribing is the clinically supervised process of dose-reducing or completely stopping medications that could cause harm or that no longer provide benefits that outweigh potential risks.[136-138] It is not an action that the patient and/or caregiver takes independent of the prescriber. It occurs under the guidance and direction of the healthcare provider. The decision to deprescribe should also be made with the patient. Forced or nonconsensual deprescribing without patients' explicit agreement is not recommended, especially for pain treatments. In particular, research is necessary on how to address deprescribing of an opioid by a provider who did not prescribe the drug. Furthermore, recognizing that older patients often have many providers due to their multiple chronic conditions, deprescribing protocols should explicitly address how responsibility will be shared for deprescribing of an opioid. Future research should therefore (1) identify what providers perceive as their set of responsibilities and locus of control, (2) develop interventions that explicitly address provider responsibility, and (3) test interventions to determine if explicitly incorporating provider responsibility into deprescribing protocols and other interventions is effective, especially in comparison with protocols that do not address how to divided or share responsibility among multiple providers. It is possible that deprescribing or tapering opioids may cause adverse events or confer a risk of harms (e.g., suicide). Research is necessary to better understand the causal effects of deprescribing and tapering approaches on harms to ensure that all approaches employed are safe in addition to being effective. Antecedent noninterventional research using secondary data might be necessary to understand the relationships between real-world discontinuation or tapering patterns and subsequent outcomes. Such information, if obtained using methods that properly account for biases (e.g., confounding and selection biases), could be valuable for informing the design of interventions. Information is also necessary to identify for which conditions deprescribing might be inappropriate because it represents a deprivation of important, medically necessary therapy. For example, deprescribing opioids for older adults with refractory dyskinesias might be highly inappropriate and result in severely impaired quality of life, extreme insomnia, and suicidal depression. Qualitative research could help to confirm that opioids are essential and equipoise does not exist for interventional research on deprescribing in such circumstances.

Research Needs Specific to Multimodal Stepped Care Pain Therapy

Research specific to older populations is necessary on the outcomes of interventions related to multimodal stepped care pain therapy—a pain treatment approach that (1) combines medications from different pharmacologic classes and (2) combines pharmacologic and nonpharmacologic therapies or multiple nonpharmacologic therapies.

In particular, research on how to implement this approach in resource-constrained clinical settings should be conducted. More evidence is also necessary to confirm that multimodal stepped therapy improves older adults' outcomes, including functioning, disability (especially related to pain), quality of life, and any other outcomes valued by older adults. While opioids are more effective if they are combined with nonpharmacologic treatments, more evidence is necessary to provide a better understanding about how, given a specific source of pain or combination of sources, different interventions should be combined and modified for older adults.[139] The number of treatment combinations is nontrivial considering that in addition to medications, multimodal stepped therapy may also include cognitive-behavioral therapy, massage, physical therapy, rehabilitation, exercise, acupuncture, meditation, and more. Since many different research questions will need to be answered to establish the role, feasible designs, and ideal implementation of multimodal and multidisciplinary care interventions for older adults, qualitative research involving key stakeholders may be necessary to establish a structured research agenda and sequential steps.

Interventions To Identify or Reduce Opioid-Related Disorders in Older Adults (Triangle I2)

Evidence Base

As listed in the second set of subrows in Table 15, we identified eight studies pertaining to identifying or reducing opioid-related disorders (including misuse). These align with Triangle I2 in the Conceptual Framework (Figure 1). Six of the studies evaluated screening tools (at the patient level) to predict risk of opioid-related disorders. While we have aligned these with Triangle I2, one could equally argue that they align with Triangle I1 (reducing opioid prescribing where harms may outweigh benefits) since the tools may be used during decision making regarding choice of treatment. Two studies (Pasquale 2017 and Rose 2016) also addressed issues related to Triangle I1 and are described in the section above (*Interventions to Reduce Opioid Prescribing*).

Screening Tools

Six studies evaluated tools to identify older adults either at risk of, or with, opioid misuse, dependence, or OUD, but only two assessed the same tool.

Park 2011[127] analyzed a validated tool (for the general population) to develop a tool specifically for older adults with chronic pain. They **modified** the existing **Pain Medication Questionnaire (PMQ)** into a 7-item version and evaluated it in 150 older adults (≥65 years) who had chronic pain (≥3 months) and were using opioids for at least 30 days. The tool was evaluated to predict opioid misuse. The authors concluded that the modified PMQ may be useful in assessing opioid misuse in community-dwelling older adults with chronic pain, but that future studies are needed to confirm the reliability, validity, and factor structure.

Tiet 2019 evaluated a 2-item instrument they had previously developed,[140] the **Screen of Drug Use (SoDU)** tool, in patients seen at primary clinics in the VA system, with a mean age of 62 years.[128] In the study cohort, 34 (2.7%) of participants met criteria for OUD. The original

purpose of the tool was to screen and identify those with any drug use disorder (including stimulants, cocaine, narcotics, hallucinogens, inhalants, marijuana, tranquilizers, and miscellaneous). Among 1,283 patients, the researchers evaluated the tool to identify OUD as diagnosed by the Mini International Neuropsychiatric Interview (MINI) structured diagnostic interview.[141] The SoDU tool was found to have perfect sensitivity (100%) and high specificity (86%). In subgroup analyses, for "older" participants (undefined, but likely >62.2 years), the tool had even higher specificity (94%). The authors concluded that the 2-item SoDU tool had excellent statistical properties and is suitable for primary care practices.

Beaudoin 2016[129] validated an existing tool, the **Prescription Drug Use Questionnaire, patient version (PDUQp)** in a set of patients known to have used opioids in the previous 30 days. The article reported on a subgroup of 38 patients aged ≥65 years. The tool was validated for opioid misuse and OUD. Henderson 2015[130] also assessed the PDUQp in 88 older adults (≥65 years) with subcritical illnesses or injuries seen in the ED who were using opioids daily. The study assessed the population for opioid misuse and "abuse." The authors concluded that the PDUQp may be a viable instrument to screen for prescription opioid misuse and OUD, but likely requires modifications to optimize its predictive ability in adults over age 50 years.

Cheng 2019[131] evaluated a different existing tool (validated in the general population), the **Severity of Dependence Scale (SDS)** in 246 older adults (aged 65-90 years) who were prolonged users of central nervous depressants, including opioids (and benzodiazepines and hypnotics). The study evaluated medication misuse or dependence (as a combined outcome), specific to opioid use (and specific to other drugs). The authors concluded that the SDS is reliable, valid and capable of detecting medication misuse and dependence among hospitalized older patients, with good diagnostic performance.

Finally, Draper 2015[132] categorized 210 older adults (≥60 years) who were receiving outpatient clinical care at an urban hospital based on their score on the **Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)** and their opioid (and alcohol and benzodiazepine) misuse status. However, only two included individuals were classified as having opioid misuse. The authors did not appear to make recommendations about the use of ASSIST and noted that there may be several important complexities with using the tool as a screen.

Two ongoing systematic reviews may be pertinent to the evaluation of screening tools in older adults. Raposo Galindo et al.[142] are conducting a systematic review of validated assessment tools for measuring the risk of behavior suggestive of opioid "abuse" in adults with noncancer pain. The review, as a whole, does not focus on older adults, but plans to focus on "different age groups" including older adults, as data allow. Listed outcomes include opioid use. The researchers planned to publish in 2018, but we found no record of the finalized review. Pask et al.[143] also have an ongoing systematic review of how opioids affect cognition in older adults (≥65 years). In particular, they are investigating which "screening and assessment tools can be used to detect and assess opioid-induced cognitive impairment in older adults," excluding those with opioid misuse. Listed outcomes include cognitive function and cognitive impairment. The researchers planned to publish in early 2019, but we found no record of the finalized review.

Clinician-Level Intervention To Reduce Misuse

As described above, Pasquale 2017[119] randomized clinicians managing patients enrolled in Medicare determined to be at increased risk for opioid "abuse" to be sent either **"patient information," educational materials for diagnosis and management of pain, both patient information and educational materials, or there was no communication.** In addition to the

lack of effect on outcomes opioid prescriptions, the study also found no effect on diagnosis of OUD. Of note, about 10 percent of patients had new diagnoses of OUD during the study.

Patient-Level Intervention To Reduce Misuse

As described above, Rose 2016[118] evaluated a **patient education pamphlet** in 172 patients undergoing major joint replacement (mean age 63). The goal of the pamphlet was to inform patients about safe opioid storage, opioid weaning, and opioid disposal. Reported outcomes included ease of weaning off opioids, opioid withdrawal symptoms, opioid disposal, opioid storage, and opioid use cessation. The authors concluded that the pamphlet improved self-reported proper opioid disposal rates in postoperative patients.

Research Needs Regarding Interventions To Reduce Opioid-Related Disorders in Older Adults (Triangle I2)

Studies of interventions that clinicians, patients, healthcare systems, or other entities can use to reduce either inappropriate opioid prescriptions or the risk of opioid misuse are sparse or lacking for older adults. Although we did not evaluate the effectiveness of interventions in the studies, overall, the reported results are not impressive, suggesting that new tools, methods, and specific interventions are needed to ensure more appropriate opioid prescribing among older adults and to minimize the risk of older adults becoming dependent on their opioid prescriptions.

Research Needs Specific to Validation of Existing Tools To Identify Opioid Misuse or OUD

Several tools have been validated and/or evaluated to identify older adults at increased risk of opioid misuse or OUD, but there has been little to no replication of findings. Validation of existing screening tools for opioid misuse or OUD in large, national populations of older adults is a clear research need to ensure that the tools are feasible to use and accurate for populations other than the small, limited ones in which the tools were developed and tested. It is also unclear to what extent many of the tools can be implemented in multiple care settings, as well as whether setting might modify the accuracy (i.e., discriminative ability) of the tools. Another key related research need is validation of the Opioid Risk Tool (ORT) and Screening, Brief Intervention, and Referral to Treatment (SBIRT) tool in older adults. Whether the findings from studies of ORT and SBIRT among younger or middle-aged adults can be extrapolated to older adults is unknown. Given the multitude of unique characteristics of older adults, it is unclear if the tools will generalize well without any modifications. It is possible that the items of the ORT are unlikely to be impacted by age, but this remains unknown without further study. Studies of the tools are particularly needed for primary care settings. Such studies should carefully document the validity and reliability in the overall population of older adults and within strata of older age (e.g., 60 to 69.9 years, 70 to 79.9 years). If an alternative tool were to be developed specifically for older adults, research should focus on the brevity of the tool as a key feature that is necessary for it to have meaningful uptake among clinicians caring for medically complex older patients in busy primary care settings.[b] An assessment of the cultural appropriateness of various tools and their performance across subgroups of race and ethnicity is a remaining research need. Given

[b] Some discordance existed among Key Informants about the generalizability of available screening tools, with some experts arguing that the screening tools developed in younger adults can be readily applied to older adults (without needing replication in studies of older adults) while others arguing that further research is necessary to adapt and validate the tools, particularly for OUD prevention.

existing evidence that suggests race and ethnicity are potentially important predictors of opioid-related outcomes, a rational next step is to study how tools (and management of opioids more broadly) might need to differ for older racial/ethnic minority adults with pain.

Research Needs Specific to Implementation and Effectiveness of SBIRT

In addition to foundational research on the implementation and effectiveness of SBIRT for OUD in older adults, there is a need for research on how to integrate SBIRT into existing care management for older adults. Medication reviews are a prime target because SBIRT could be integrated into regular medication reviews for older adults. How exactly this should be done, though, remains empirically unstudied. Research identifying the optimal and most effective ways to combine SBIRT with medication reviews and other routine care management is highly important. There is also a need for more empirical evidence about which medications (methadone, buprenorphine, naltrexone) and treatment regimens for OUD are most effective and safe for older adults. A related need is information on how to implement SBIRT and medications for OUD in settings where older adults often receive care, but that may not have the necessary resources or infrastructure to implement interventions to treat OUD in older adults. Post-acute care settings like skilled nursing facilities and nursing homes are likely to be one such setting.

Research Needs Specific to Provider Perception of OUD Risk

We did not identify any studies documenting providers' beliefs about OUD risk in older adults. Providers may prescribe opioids long-term to older adults because they believe that the risk of OUD is particularly low in this population, especially considering the marketing materials providers received from pharmaceutical companies in the 1990s and possibly beyond suggesting that OUD and addiction risk were low. Qualitative, survey, or other research may necessary to empirically document provider beliefs and understand provider perceptions. These perceptions may be an important predictor of prescribing and opioid-related harms. If true, that information could eventually inform the development or tailoring of behavioral interventions aimed at reducing suboptimal opioid prescribing for older adults. Key Informants also noted that many caregivers and patient family members do not believe older adults are at a high risk, or any risk, of misusing opioids or developing OUD. These beliefs and perceptions could be very important to study as potential predictors of misuse and OUD as they would inform future interventions attempting to incorporate caregivers or family members into misuse or OUD surveillance efforts. The perceptions and beliefs of various stakeholders are also important because they might result in erroneous expectations about the effects of mandatory system-wide interventions to reduce opioid prescribing. While such system-wide interventions could potentially reduce the risk of OUD across all age groups, they might also result in significant harms to older adults who require opioids and are unable to substitute alternative nonopioid treatments.

Research Needs Specific to Care Coordination

Research is needed on whether interventions to improve care coordination between providers can help to reduce misuse and OUD (and also opioid-related harms). The lack of communication about what medications are being prescribed by providers in one setting to providers in other settings can either directly result in harms (e.g., through therapeutic duplication resulting in overdose) or facilitate opioid misuse. Research on how interventions to improve coordination between an older adult's primary care provider and other providers (i.e., collaborative capacity) impact the risk of opioid misuse and OUD is particularly necessary. A better understanding of the characteristics of one provider in relation to another will likely need to accompany research

on communication; in particular, understanding the relationship between co-location or geographic proximity of primary care, pain management, mental health, and substance use services. Finally, the development of integrated approaches or interventions involving healthcare (e.g. pharmacists) and social care (e.g. social workers) professionals may help to prevent problematic opioid use or to identify it earlier than would have been possible otherwise.

Research Needs Specific to Safe Storage and Disposal

While we found a single study about educating older adult opioid users about safe handling of opioid prescriptions, further evaluation of safe storage and disposal programs to reduce opioid misuse may be a topic for future examination in research studies.

Interventions To Reduce Opioid-Related Harms (Triangle I3 and Rectangle F)

Evidence Base

Two studies evaluated interventions designed to reduce opioid-related harms (as shown in the last rows of Table 15). Both studies evaluated interventions aimed at clinicians, one set of interventions was designed to reduce opioid misuse (and related harms) among Medicare patients deemed to be at high risk, and the other was an intervention to manage opioid misuse in older adults.

Clinician-Level Intervention To Reduce Misuse

As described above, Pasquale 2017[119] randomized clinicians managing patients enrolled in Medicare determined to be at increased risk for opioid "abuse" to be sent either **"patient information," educational materials for diagnosis and management of pain, both patient information and educational materials, or there was no communication.** In addition to the lack of effect on outcomes opioid prescriptions and risk of new OUD, the study found no effect of the interventions on risk of opioid-associated ED visits.

Clinician-Level Intervention To Manage Opioid-Related Disorders

The only study that pertained to management of older adults with opioid misuse, Chang 2019,[133] was an evaluation of **motivational interviewing training** for 31 doctorate of nursing practice students. The training used as an example a hypothetical older adult who took more prescription opioids than prescribed (thus, misuse), and then evaluated the students' motivational interviewing knowledge, confidence, attitude, skills, and their substance "abuse" knowledge. The authors concluded that the preliminary findings suggested motivational interviewing education with standardized patient simulation could improve nursing students' knowledge of and confidence in motivational interviewing techniques to manage prescription opioid "abuse" among older adults. The study did not measure the effect of the educational approach on subsequent clinical practice or older adults' outcomes.

Patient-Level Interventions To Manage Opioid-Related Disorders

Of note, a systematic review, by Wylie et al.,[144] is ongoing and evaluating opioid agonist therapy in older adults. However, it is unclear whether the review is specifically addressing interventions. Their protocol describes the goal "to gain an understanding of older adult (50+) service user experiences during opioid agonist therapy" and to "assess the [opioid agonist therapy] experiences of older adults with an opioid disorder." Their reported primary outcomes include "the identification of the facilitators, barriers, incompatibilities and potential areas for

improvement of [opioid agonist therapy] for an older adult population." They expect to publish their results in 2019, but we have found no record of the finalized review.

Research Needs Regarding Interventions To Reduce Opioid-Related Harms (Triangle I3 and Rectangle F)

Research Needs Specific to Tools To Predict Harms During Appropriate Opioid Use

Distinct from validation of existing tools to identify misuse or OUD (addressed in the prior section pertaining to Triangle I2 in the Conceptual Framework), tools are necessary to help providers identify older adults who are likely to experience opioid-related adverse events despite using opioids appropriately (which address Triangle I3 in the Conceptual Framework). While the evidence map suggests some potential tools may exist for identifying opioid misuse and related harms that occur during misuse, we identified no person-level screening or prediction tools that attempted to identify older adults who were most likely to experience an opioid-related harm despite using opioids as prescribed by a provider. Accordingly, there were no tools that explicitly calculated the tradeoffs between expect benefits and harms to derive a benefit-harm ratio for a given person. Research is necessary to develop these tools, which are foundational for expanding efforts to avoid or mitigate adverse events when an older person truly requires opioids for pain management. In addition to research that helps to answer how benefits and harms should be assessed, research is also necessary to identify exactly who is poised to best perform the benefit-harm assessment. It is possible that some individuals may become well-poised to assess the balance of benefits and harms of opioids through education or formal educational interventions. Families and caregivers, for example, might be such persons. Clinicians, direct care workers, health profession students, and faculty are likely to be identified as persons for whom educational interventions might be impactful. Educational intervention studies should focus on training these individuals to quantify the benefits and risks of opioids, and then reduce opioid prescribing where harms outweigh benefits. They will also need to train individuals to better understand how to increase access to nonopioid treatments, prevent opioid misuse or OUD, and reduce the risk of opioid-related harms when opioid use is necessary. Educational interventions focused on helping social care providers (e.g., social workers) to screen, assess, and diagnose substance use disorders among older adults might be particularly impactful for identifying opioid misuse or OUD.

Research Needs Specific to Self-Management

Self-management is becoming a more prevalent component of pain treatment approaches. This raises important questions how self-management (and interventions more broadly) might need to be adapted for older adults, especially those with cognitive impairment or other challenges to self-management. The challenges that cognitive impairment and dementia might pose are unique to the older adult population and are a major and important challenge that prevents generalizing evidence from younger cognitively-intact populations to older ones. A particular program, the Chronic Pain Self-Management Program (CPSMP), may be in use by some National Aging Network partners, but studies were not identified in the evidence map that report on the effectiveness or outcomes of this program in an older adult population.[3] Studies of the outcomes of CPSMP may help advance our understanding of the role of self-management in improving opioid prescribing for older adults.

Research Needs Specific to Settings for OUD Treatment

There is no empirical information about management of older adults with opioid misuse or OUD, and, more specifically, the comparative effectiveness of various settings for treatment of OUD for older adults. Standard outpatient versus more controlled residential treatment facilities are both options for OUD treatment and provision of medication assisted treatment, but the comparative effectiveness of these settings, especially when taking into account the severity of older patients' OUD or medical complexity, is unknown. Each setting and the way they provide medication assisted treatment may have important differential effects on subsequent outcomes, including relapse prevention. More information is also necessary to understand whether certain settings are more effective for specific subgroups of older adults. For example, while more research is necessary in general about the management of OUD for diverse racial and ethnic minority older adults, research might be particularly helpful on which settings result in the best outcomes for racial/ethnic minority older adults with OUD.

Research Needs Specific to Naloxone Kits

While emergency naloxone rescue kits are now recommended for all patients receiving medication assisted treatment, research is necessary to confirm that older adults have also been receiving these kits. Perhaps even more importantly, research is necessary to understand how family members and other caregivers are engaged and educated about the use of these kits. Older adults often have complex caregiving circumstances and unique strategies may be necessary to engage all of their caregivers in opioid overdose prevention through education or other means. In the event of an overdose, it is unclear if caregivers are prepared to use the rescue kit.

Research Needs Specific to Care Coordination

As suggested by other portions of the conceptual framework and evidence map, interventions that organize multiple providers from different specialties or disciplines and provide training in pain medicine or related principles are likely to be particularly fruitful topics for future research. Poor pain-related care coordination is a likely driver of hospitalizations and ED visits. The development and assessment of interventions that improve care coordination for older adults with pain may therefore reduce the risk of opioid-related hospitalizations and ED visits.

Research Needs Specific to Tailoring Opioid-Related Information

Since providers need to discuss the benefits and risks of opioids with their older patients, but have little information about how benefits and risks may manifest and result in a future opioid-related hospitalization or ED visit for a particular patient, research is necessary on how to individualize and tailor information about opioids during discussions with older patients, both prior to starting opioids and while they are continued. The provision of relevant information or education may help older patients avoid hospitalizations or ED visits by avoiding or minimizing the adverse events of opioids. An important area of future research might explore how best to provide patients with information about their opioid prescription (e.g., with follow-up phone calls made by a pharmacist or health professional) and what information might be most relevant (e.g., information focused on modifiable patient risk factors like alcohol use and how to avoid falls).

Research Needs Specific to Coprescribing and Polypharmacy Tools

Screening for coprescribing and drug-drug interactions alone is an important component of efforts to reduce opioid-related hospitalizations and ED visits among older adults. Research is

necessary to formally develop and validate screening or prediction tools to quantify the risk of opioid-related events due to coprescribing, drug-drug interactions, and polypharmacy. This is especially true for circumstances where older adults are taking medications as prescribed (i.e., not misusing opioids). Key Informants noted that some providers simply screen for coprescribed medications or drug-drug interactions (usually followed by stopping ≥1 medications or modifying treatment regimens) as their primary approach in clinical practice to reduce opioid-related hospitalizations or ED visits. Research would be helpful to develop a systematic interventional approach that formalizes this practice and examines its effectiveness using the outcome measure of subsequent risk of opioid-related ED visits or hospitalizations.

Research Needs Specific to Other Opioid Outcomes

It is possible to take a broader view on what constitutes an "opioid-related" hospitalization or ED visit. Beyond respiratory depression and overdoses, opioids have been associated with a variety of outcomes, many of which are surprisingly understudied. For instance, high-quality empirical evidence on motor vehicle crashes associated with opioid use is surprisingly scarce. Beyond overdoses and respiratory depression, further research on some of these opioid-related events that result in hospitalizations or ED visits could result in novel interventions, such as programs that intervene to balance an older adult's need to drive for mobility against their need to take opioids for pain management. Suicide, violent deaths, falls and other injuries may all be particularly valuable foci for future studies.

Research Needs Specific to Peer Support and Mutual Help Meetings

Narcotics Anonymous (NA) and other mutual help meetings are popular sources of support for individuals who use illicit opioids like heroin. The role of NA and other mutual help meetings or organizations is poorly understood for older adults with OUD. The social support provided through those venues could have a beneficial effect on outcomes. More research is necessary to understand the role of NA or similar organizations in the care of older adults with OUD. Related to NA and mutual help, more research is necessary about the effects of peer support programs, which have been employed to engage and retain middle-aged adults in substance use disorder and mental health treatment, but for which no studies were identified by the evidence map for older adults.

Research Needs Specific to Recovery

No studies of older adults were identified that addressed recovery—the process of change through which older adults overcome their OUD, regain their health and social function, and live self-directed lives while reaching their full potential. It is thus unknown whether recovery support services for OUD exist for older adults and if they are effective. Additionally, identifying the features of such services that might best promote recovery is a major research need. For example, older adults often have important individual needs and strong unique preferences; interventions that reflect these may be more effective at promoting engagement in OUD treatment and recovery from OUD among older adults.

Other Research Needs Pertaining to the Management of Opioid Use in Older Adults

Although our evidence review did not cover several of the topics below, there were clear needs to fill gaps in knowledge about them to address the topic of the review. Many of these needs directly or indirectly relate to Rectangle C in the Conceptual Framework.

Research Needs Specific to Management of Cancer Pain for Older Adults

Experts believe that older adults with cancer and those at end-of-life frequently require opioids for pain management. However, there are concerns among stakeholders that many providers consider cancer as a condition that provides an exemption from the application of pain management principles; in particular, for individuals who have treatable cancers versus those for whom cancer is end-stage. As a result, cancer patients may not receive an adequate examination of the cause of their pain. For example, some older adults with cancer may have neuropathic pain from the malignancy while others may have postsurgical pain, each of which might respond better to different treatments. Furthermore, providers may be more willing to prescribe opioids and to prescribe them at higher doses than they ordinarily would for patients without cancer. Individuals with cancer are excluded from some opioid prescribing guidelines.[139] Prescribing guidelines that are not specific to older adults do exist for individuals with cancer.[145] Research is likely necessary to understand whether cancer presents a unique set of factors that influence opioid prescribing and outcomes, and if yes, to ultimately develop more rigorous pain assessment tools to guide opioid prescribing for older adults with cancer.

Research Needs Specific to Comparative Effectiveness of Opioids and Nonopioids in Older Adults

Our evidence map did not include studies that evaluated the effectiveness of interventions to reduce pain, *per se*. However, discussions with stakeholders raised several concerns about the lack of evidence regarding which interventions are adequately, or most, effective to treat pain in older adults. The following research needs discussions are primarily based on those discussions.

Research is necessary to fill the gap in knowledge about the comparative effectiveness of opioid versus nonopioid interventions in older adults. Selecting nonopioid therapies in place of opioids requires comparative effectiveness and safety evidence that is lacking, especially for nonpharmacologic interventions. Research to develop tools or algorithms that help providers better understand which of their older patients are likely to derive benefits from opioids in excess of any harms, especially compared to nonopioid alternatives, is also lacking. Some of this research has been recently funded (in September 2019) by the National Institutes of Health (NIH), in part under the Helping to End Addiction Long-term (HEAL) Initiative launched in April 2018, and results will become available in coming years, though these studies were not considered for the current technical brief. These investments by NIH in understanding the role of nonopioid and nonpharmacologic treatments is important and will likely be relevant for older adults. Nonetheless, research may still be necessary to answer questions such as "What are the unintended harms of implementing mandatory system-wide interventions to reduce opioid prescribing and substitute alternative nonopioid treatments?" It is highly important to study the premise that increased access to nonopioid treatments will prevent or reduce suboptimal opioid use. For many subpopulations of older adults, the premise may be false and system-wide interventions may cause considerable harm if they do not exempt such subpopulations. Therefore, in addition to understanding the comparative effectiveness of opioids and nonopioids in older adults, research is necessary to both identify subgroups of older adults for whom long-term opioid may be the only viable option and how to best ensure that system-wide interventions do not mistakenly attempt to replace their opioid therapy with inviable nonopioid therapies.

Research Needs Specific to Adapting Nondrug Interventions for Older Adults and Frail Patients

A broad knowledge gap exists about what, if any, evidence on interventions in younger adults is transferrable to older adults or can be tailored to meet the specific needs of older adults. In particular, research will likely be necessary on how to adapt nondrug (and, thus, nonopioid) interventions for the older adult population. For example, exercise, physical therapy, and complementary and alternative medicine interventions studied in younger adults will likely require geriatric modifications, especially for older adults who are frail, multimorbid, or have disability and functional limitations. These medically complex older adults are often excluded from most randomized controlled trials of drug and nondrug interventions, even among those that included older adults. Therefore, frail individuals and those with multimorbidity should be a crosscutting focus of many future research studies. In particular, more research is needed on cognitive behavioral therapy for pain in older adults to answer questions about how it might work (i.e., the mechanisms underlying any observed effects), how it should be combined with exercise and other therapies in a multimodal treatment approach, and how multidisciplinary teams can successfully incorporate principles of cognitive behavioral therapy into their clinical practice.

Research Needs Specific to Cost and Reimbursement of Nonopioid Therapies

Major cost barriers may exist to accessing nonopioid therapies, especially nonpharmacologic ones. Most of these (e.g., massage therapy) are often not reimbursed by insurers. If they are reimbursed, patients may frequently be responsible for paying a large proportion of the cost out of pocket. Evidence was unavailable about how interventions to improve access to nonpharmacologic therapies might be implemented and what the effects on patient utilization and outcomes would be among older adults. Along with comparative effectiveness and safety research, information on reimbursement and access to nonpharmacologic therapies is fundamentally necessary to decrease opioid use through the substitution of alternative therapies. Additionally, research into how older adults' income, financial assets, and socioeconomic status influence use of nonpharmacologic therapies may also be necessary. Such information could be used to identify older adults who are forced to select alternative interventions that are relatively more affordable (e.g., cannabis or marijuana) and target interventions to them. Finally, research is necessary on the costs of opioid misuse and OUD at the individual and society levels, though this topic was outside the scope of the current report. Cost could be studied as either as an outcome of nonopioid therapy use (e.g., cost savings through avoidance of misuse or OUD) or as a stand-alone topic.

Research Needs Specific to Marijuana and Cannabis as Cointerventions

Greater research is likely necessary to understand the role, if any, that cannabis and marijuana have in a pain treatment plan for older adults. Comparative effectiveness research focused on comparing the safety and effectiveness of cannabis/marijuana and other therapies is likely a key area for future research. This need exists partly because some older patients perceive cannabis and marijuana as being more readily accessible than other nonopioid therapies like acupuncture, especially in terms of cost, since many insurers do not cover acupuncture, massage, and other alternative nonopioid therapies. Research into the safety of combining opioids and cannabis is likely also urgently necessary since older adults are currently combining these substances on their own.

Research Needs Specific to Goal-Setting and Shared Decision Making

Tools have not been reported that could explicitly help providers establish opioid-related treatment goals for pain, function, and other relevant outcomes through shared decision making with their older patients or caregivers. Such tools could, in theory, help to avoid opioid prescribing entirely or promote the use of lower and/or less frequent doses. Evidence is also necessary to address how providers and patients should come to an agreement about when opioid use should be stopped, how often that plan or agreement should be discussed, and to what extent patients might self-manage their opioid regimen to make adjustments in response to inadequate pain relief or adverse events without engaging in misuse. Related to goal-setting and shared decision making is the need to identify how to best measure the outcomes of pain management that are of utmost importance to older adults. In particular, research on outcome measures that relate to older adults' goals of pain treatment could help to optimize opioid use and pain treatments more broadly. Some older adults have more severe pain at times when they must be more active or mobile (e.g., when they must transfer into or out of a wheelchair), yet few studies have examined outcomes like transfers or the ability to perform activities of daily living without pain. Such outcomes are essential for understanding when opioids might provide benefits that outweigh harms, and are important to older adults. More research is also necessary to understand the effectiveness of dosing strategies that maximize patient-centered outcomes; for example, research to understand the comparative effectiveness of taking opioids at times when more mobility or activity is necessary versus taking opioids at scheduled times regardless of activities of daily living or other activities that might increase the presence or severity of pain.

Additional Pertinent Ongoing Research

In fiscal year 2019 alone, several hundred studies of opioids have been funded by the NIH. Many of these studies were funded through the NIH HEAL Initiative that coalesced in April 2018.[146] The studies covered by this initiative address different aspects of opioid use and misuse across a wide variety of populations. These newly funded studies were not considered for the current technical brief unless they had registered in ClinicalTrials.gov between the years 2000 and 2019. The number of newly funded studies that specifically address older adults is therefore unclear. However, it is important to note that these investments by the NIH are likely to advance our understanding of different subtopics address by this current report. For example, projects have been funded to optimize new targeted, nonaddictive medications and nonpharmacological treatments for various types of pain, which could be highly relevant for older adults with limited treatment options due to prevalent comorbidities and contraindications. Some of this research might also provide information about the comparative effectiveness of opioid and nonopioid therapies on outcomes of high importance to older adults, such as quality of life and functioning. Other funded projects might provide more information about cognitive behavioral therapy for pain, including the mechanisms underlying how it works, how to combine it with other treatments (e.g., exercise, stress management), and who can successfully implement it (e.g., physical therapists, psychologists, nurse practitioners).

On August 31, 2018, the Centers for Disease Control and Prevention (CDC) provided over 150 million dollars to U.S. states and territories to address opioid overdose with the explicit goals of advancing the understanding of the opioid overdose epidemic and scaling up prevention and response activities to make an immediate impact and save lives.[147] Several of these grants may address relevant subtopics that are the focus of this technical brief. For example, under RFA-CE-18-004, "Research to Evaluate Medication Management of Opioids and

Benzodiazepines to Reduce Older Adult Falls," more information is likely to become available in coming years about how to taper or discontinue opioids in older adults to reduce falls and unintentional injuries.

Summary and Implications

Summary of Conceptual Framework and Evidence Base

As part of this technical brief on prevention, diagnosis, and management of opioid use, misuse, and opioid use disorder in older adults, we created a Conceptual Framework that outlines the stages of care for older adults who use (or may use) opioids and factors that impact management decisions and patient outcomes, including assessment of pain, selection of pain treatment, choice of opioid regimen, assessment for opioid misuse or OUD, and management of misuse or OUD (Rectangles B to F in the Conceptual Framework, Figure 1). Multiple potential patient, provider, and societal predictors (Ovals P1 to P8) may influence opioid-related harms and other outcomes, and the Framework at large. Predictors and interventions to reduce opioid prescriptions where harms outweigh benefits (Octagon R1 and Triangle I1), prevent opioid misuse and OUD (Octagon R2 and Triangle I2), and reduce other opioid-related harms (Octagon R3 and Triangle I3) are included.

This broad overview of the evidence base identified 41 studies with multivariable models of factors associated with opioid-related outcomes. We believe it is likely that only (or mostly) the multivariable analyses could provide adequate evidence that putative factors are likely to be reliable predictors of outcomes. The studies addressed one outcome (long-term opioid use) related to factors that are predictors of opioid use (Octagon R1 in the Conceptual Framework), two sets of outcomes (opioid misuse and multiple opioid prescribers) related to factors that are predictors of opioid use or OUD (Octagon R2) and four sets of outcomes (mental or physical harms, hospitalizations or ED visits, opioid overdose, and death) related to factors that are predictors of opioid related harms (Octagon R3).

The largest body of evidence (22 studies) evaluated factors associated with long-term opioid use. Of note, however, is that the outcome long-term opioid use does not address whether the harms associated with use outweigh the benefits. Long-term use may be a poor proxy for potential harms or problematic opioid use and may simply be an indicator of incomplete treatment of the underlying condition causing pain and thus long-term need for pain control. Nevertheless, the studies were consistent (in full agreement) that opioid use prior to surgery or injury (or early use after surgery) and greater amount of opioids (more prescriptions or higher dose) are the factors with mostly strong associations. Other consistent associations, but with largely weak associations, were found with back pain, depression, concomitant NSAID use, and fibromyalgia. Studies were mostly consistent (≥75% agreement) that benzodiazepine use, higher comorbidity scores (such as the Charlson Comorbidity Index), "substance misuse" (although, generally poorly or not defined in studies), tobacco use, and low income were associated with long-term opioid use. Studies were also mostly consistent that alcohol "abuse" and healthcare utilization were *not* associated with long-term opioid use. Factors with variable findings of association included gender, age among older adults, Black race, dementia, rural or nonurban residency, prescription of long-acting opioids, unmarried relational status, and use of muscle relaxants.

Across six studies of factors associated with developing opioid-related disorders, three studies each had variable findings regarding the associations of alcohol misuse and of gender with opioid misuse. All other evaluations of specific associated factors and outcomes of interest were evaluated by only one or two studies each. These included analyses of opioid use disorder, high-risk obtainment of prescription opioids, procuring multiple opioid prescribers, mental health outcomes, physical health outcomes, all-cause hospitalization, opioid-related hospitalization,

nonopioid-specific hospitalization, emergency department visits, opioid overdose, all-cause death, opioid-related death, and nonopioid-related death.

Only 16 studies addressed interventions of any kind to appropriately reduce opioid prescriptions (Triangle I1 in the Conceptual Framework, 9 studies), prevent opioid-related disorders like OUD in older adults (Triangle I2, 8 studies), or reduce opioid-related harms (Triangle I3, 2 studies). The most-studied interventions (in 6 studies) are screening tools to predict opioid-related harms but none has been tested in clinical practice to assess real-world results. Two studies found that PDMPs are associated with less opioid use (at the State level), although they did not address the effect of the PDMPs on patients (e.g., their level of pain control). Other studied interventions to reduce opioid use included a patient-level pain rehabilitation program and a patient-education pamphlet, different clinician-level educational modalities, a hospital system-level opioid safety initiative, provision of free (to patient) acetaminophen, and a nationally-mandated tamper-resistant opioid formulation. Few studies evaluated the parallel effect of the interventions on patient-centered outcomes, including daily functioning or activities of daily living, disability, quality of life, and pain control. One study each evaluated clinician- and patient-level educational materials. With the goal of reducing opioid-related harms, one study evaluated motivational interviewing training of nursing students to help manage older adults with opioid-related disorders and one study evaluated clinician-level educational materials. Of note, the recreational pathway (Box A2) was not specifically addressed by the empirical evidence.

Future Research Needs

As noted, there are many gaps in the evidence base regarding factors associated with opioid-related outcomes and of the effectiveness of interventions for older adults. We describe numerous research needs derived from clear gaps in the evidence base and based on issues raised by a range of stakeholders. In particular, future research should emphasize the adaptation of existing interventions for use in older adults, account for the heterogeneity in characteristics of the older adult population, incorporate outcomes of greatest importance to seniors, and determine how caregivers can help to actively implement interventions. To date, all studies have evaluated groups of older adults with little if any attempt to parse out benefits and harms among subgroups (e.g., by age within the category of "older adults," by generational cohort, or by underlying condition). As a precursor to that work, it may be necessary to define "older adult" in a principled way and better understand the relationship between age, period, and birth cohort. The question of how to deprescribe opioids safely, especially when individuals are dependent on opioids and experiencing pain, is especially complex in older adults and deserves a special focus. Studies among older adults to confirm the reliability, validity, and factor structure of screening tools for detecting opioid misuse are an especially salient and attainable next step. The development, validation, and evaluation of new interventions tailored to the needs of older adults will likely also be necessary to manage opioid misuse and OUD in older adults.

Limitations

We developed an evidence map to describe the amount and type of practically available evidence related to the core of the Conceptual Framework, but in keeping with the scope of a Technical Brief, we did not fully assess studies (e.g., their risk of bias) or the body of evidence (e.g., strength of evidence). For feasibility, we did not consider research published more than 20 years ago (specifically, earlier than 1/1/2000), because older empirical data are less likely to be

relevant to today's setting. Demographic and clinical characteristics of older adults have shifted dramatically over the last 20 years, so earlier evidence may not generalize well to a modern older adult population. Where earlier studies may also be applicable, important questions are often addressed by more recent replication studies, in which case they would be represented in the evidence map (with the possible exception of studies of pharmacological interventions, such as for treatment of OUD, that have not recently been investigated in older adults).

It is important to note that we did not review articles to determine whether they would meet any specific set of eligibility criteria for a systematic review of a specific Key Question. In our estimation, it is likely that many of these articles would be rejected for a given systematic review based on the specific populations of interest, the eligible definitions of predictors (or risk factors) and outcomes, study design features, and analytic methods. For example, although we assessed whether studies performed a multivariable (versus univariable) analysis when examining factors associated with opioid-related harms, we did not assess whether studies adequately controlled for all potentially important covariates in a given multivariable model. Thus, it is likely that many studies we identified in the evidence map would not be relevant to address a specific, well-formulated research question. Furthermore, the reader should be reminded that our literature search, screening, and eligibility criteria did not allow for us to delve into the large number of studies that did not focus on older adults or opioids that may have had relevant, potentially eligible, subgroup analyses. If the abstract provided no indication of an analysis regarding opioid use in older adults, it was not included. Undoubtedly, we thus missed pertinent studies that would have required more in-depth searching and screening.

While we did include studies conducted in other countries besides the U.S., we restricted to those countries with high-income economies where opioid misuse and OUD were anticipated as being most prevalent.

Finally, we did not include studies of older adults in palliative care, those who were terminally ill, those in hospice care, or others with limited life expectancy because opioid misuse, harms, or OUD were of significantly less concern in such populations. This should not be interpreted as a suggestion that these populations are not important.

Conclusions

Prevention, diagnosis, and management of opioids, opioid misuse and OUD in older adults are significant and challenging issues for which a greater understanding is necessary. The evidence base that is directly applicable to older adults who are prescribed opioids or have opioid-related disorders is sparse. Fundamental research is necessary to determine which factors may predict opioid-related harms; studies to date suggest that the amount of prescribed opioids, prior use of opioids, musculoskeletal conditions, and substance misuse are potentially important factors. Research is also needed to identify interventions to reduce opioid treatment where harms outweigh benefits, to reduce opioid-related harms and disorders, and to treat existing misuse or OUD among older adults. The preponderance of evidence has evaluated the "risk" of long-term opioid use without evaluation of whether such use is appropriate (e.g., to manage ongoing pain) or indicative of misuse. Similarly, current studies of interventions have focused largely on quantities or duration of opioid use, without assessment of whether pain is being adequately managed. Future research should emphasize the adaptation of existing interventions for use in older adults and account for the heterogeneity of the older adult population with a goal of allowing evidence-based personalized healthcare. However, the development, validation, and

evaluation of new interventions tailored to the needs of older adults will likely also be necessary to manage opioid misuse and OUD in older adults.

In summary, two immediately actionable next steps are (1) to conduct additional research focused on predictors of and interventions to improve clinically-important, patient-centered outcomes (not only amount or duration of opioid use), and (2) to further validate and adapt screening tools for identifying opioid misuse in older adults. Intermediate-term next steps should include developing interventions to (1) increase the uptake of best practices for safer opioid prescribing that does not compromise pain control in older adults, (2) overcome barriers to screening for opioid misuse and OUD in older adults, and (3) expand treatment for OUD in all settings where older adults receive care. Ultimately, developing the evidence base will enable policymakers, healthcare providers, and older adults to reduce inappropriate opioid use and the harms associated with opioid use and misuse.

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Abbreviations

This list of does not include abbreviations used only in tables or figure.

AHRQ	Agency for Healthcare Research and Quality
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
CDC	Centers for Disease Control and Prevention
COPD	chronic obstructive pulmonary disease
CPSMP	Chronic Pain Self-Management Program
CR	controlled release
ED	emergency department
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
HEAL	Helping to End Addiction Long-term
NA	Narcotics Anonymous
NIH	National Institutes of Health
NSAID	nonsteroidal anti-inflammatory drug
ORT	Opioid Risk Tool
OUD	opioid use disorder
PDMP	prescription drug monitoring program
PDUQp	Prescription Drug Use Questionnaire, patient version
PMQ	Pain Medication Questionnaire
SBIRT	Screening, Brief Intervention, and Referral to Treatment
SDS	Severity of Dependence Scale
SoDU	Screen of Drug Use
TKA	total knee arthroplasty (replacement)
TOO	Task Order Officer
VA	Veterans Affairs

Appendix A. Search Strategies

PubMed run 7/9/19
("Opioid-Related Disorders"[Mesh]
OR "Prescription Drug Misuse"[Mesh]
OR (("Analgesics, Opioid"[Mesh] OR Opioid* OR opiate* OR opium OR "Methadone"[Mesh] OR methadone OR "Narcotics"[Mesh] OR Narcotics OR "Morphine Derivatives"[Mesh] OR Codeine OR Hydrocodone OR Oxycodone OR Dihydromorphine OR Ethylmorphine OR Hydromorphone OR Morphine OR "Prescription Drugs"[Mesh] OR Prescription Drug*) AND (abuse OR misuse OR dependence OR addiction OR diversion OR "use disorder" OR "Drug-Seeking Behavior"[Mesh] OR "long term use" OR "nonmedical use" OR "non-medical use" OR multiple providers OR multiple prescriptions)) NOT (("Alcoholism"[Mesh] OR "Benzodiazepines"[Mesh] OR "Heroin Dependence"[Mesh]) NOT ("Opioid-Related Disorders"[Mesh] or Opioid*)))
AND
("Aged"[mesh] OR "elderly"[tw] OR "elder"[tw] OR "elders"[tw] OR geriatr*[tw] OR "Homes for the Aged"[mesh] OR "Health Services for the Aged"[mesh] OR older person*[tw] OR old person*[tw] OR older patient*[tw] OR old patient*[tw] OR "older women"[tw] OR "old women"[tw] OR "older men"[tw] OR "old men"[tw] OR old adult*[tw] OR older adult*[tw] OR "Older individual"[tw] OR "Older individuals"[tw] OR "old people"[tw] OR "older people"[tw] OR "Oldest Old"[tw] OR "Nonagenarians"[tw] OR "Nonagenarian"[tw] OR "Octogenarians"[tw] OR "Octogenarian"[tw] OR "Centenarians"[tw] OR "Centenarian"[tw] OR "septuagenarian"[tw] OR "septuagenarians"[tw] OR "Aging"[mesh] OR "aging"[tw] OR "ageing"[tw] OR "older population"[tw] OR "aging population"[tw] OR "aging population"[tw] OR "age factors"[Mesh] OR "Aged, 80 and over"[Mesh] OR medicare)

6171 citations

CINAHL/PsycINFO run 7/9/19
(Opioid* OR opiate* OR opium OR methadone OR Codeine OR Hydrocodone OR Oxycodone OR Dihydromorphine OR Ethylmorphine OR Hydromorphone OR Morphine OR Prescription Drug* OR Narcotic*) AND (abuse OR misuse OR dependence OR addiction OR diversion OR "use disorder" OR "Drug-Seeking Behavior" OR "long term use" OR "nonmedical use" OR "non-medical use" OR multiple providers OR multiple prescriptions)
Narrow by SubjectAge: - aged: 65+ years
Narrow by SubjectAge: - aged (65 yrs & older)

2416 citations

Prospero run 8/27/19
(opioid OR opiate OR "prescription abuse" OR diversion) AND (older OR elderly OR aged OR old OR veteran OR medicare OR medicaid) AND (older or elderly or aged or old or veteran or medicare or medicaid)

ClinicalTrials.gov run 8/27/19
Opioid OR Prescription Drug Abuse
Age 65+

Appendix B. Additional Description of Methods

Methods

The following four Guiding Questions were developed by AHRQ in consultation with other federal agencies. After discussion wit the Key Informants, the phrasing of the questions was revised and simplified, as presented in the main report.

Guiding Questions

1. What are the most important factors driving the increase in opioid-related hospitalizations and ED visits for older adults and what interventions are needed to reduce the risk of opioid-related adverse events, opioid misuse, and opioid use disorder (OUD) in older adults without compromising pain control or quality of life?
    a. Are there interventions developed for the general population that could be applied to older adults without modification?
    b. Are there interventions developed for the general population that could be studied in older adults?
    c. Is there a need for interventions specifically designed or adapted for older adults?
    d. What outcomes should be captured specifically for older adults (falls, cognitive function, cardiovascular events, etc.)?
2. Among older patients taking opioids, what factors are most strongly associated with harms from opioids (adverse events, misuse, or opioid use disorder)?
    a. Underlying patient factors, such as fall risk, cognitive impairment, frailty, liver disease, etc.
    b. Medication factors (opioid dosing and preparation; co-prescribing; etc.)
    c. Environmental factors (presence of a caregiver, etc.)
3. What interventions have been studied to help providers—
    a. reduce opioid prescription where harms outweigh benefits in older adults without compromising pain control or quality of life (e.g., shared decision-making)?
    b. reduce the risk of adverse events, misuse or opioid use disorder in older adults for whom opioids are appropriate?
    c. identify opioid misuse or opioid use disorder in older adults?
    d. treat opioid misuse or opioid use disorder in older adults, including facilitating transitions across the continuum of care and across institutional and community settings?

   For each subquestion, describe studies by the following populations and settings:
    - Different care scenarios (acute, chronic, cancer)
    - Age, sex, race/ethnicity, income, and geography (urban, rural)
    - Settings (inpatient, primary care, long-term care)
    - Early versus late onset OUD
4. What studies are needed to develop evidence based interventions (for providers, patients, or systems) to reduce opioid prescription where harms outweigh benefits, misuse, and opioid use disorder in older adults? What should the design of these studies be?

To address the issues raised by the Guiding Questions, we developed a conceptual framework informed by stakeholder (Key Informant) discussions and conducted an evidence

map of the existing evidence base. The conceptual framework and evidence map summarize the evidence in a way that allows stakeholders to readily identify the next steps for research on opioid use and misuse in older adults.

Development of Conceptual Framework

Initial Development

A draft conceptual framework was developed based on existing prior conceptual frameworks and systems maps, including ones from Wakeland and colleagues,[38,39] the U.S. Department of Health and Human Services Pain Management Best Practices Inter-Agency Task Force Report,[40] and the National Academies of Sciences Engineering and Medicine text Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use.[41] Existing frameworks and systems maps from obesity and other conditions not directly related to pain were considered to help inform alternative structures and formats for the framework.[42,43] The draft conceptual framework was revised based on feedback from a panel of invited Key Informants.

Key Informants

We formed a 15-member panel comprised of six individuals employed by federal agencies and nine individuals employed by non-federal entities. These individuals included experts in the care of older adults, experts in pain treatment and opioid use, nationally and internationally recognized researchers, policy makers, and internationally recognized advocates for older adults with pain.

There were several stakeholder types that we explicitly sought non-federal Key Informants to represent. These individuals were selected based on their complementary perspectives on potential predictors of opioid-related harms and interventions to reduce harm among older adults.

To form our panel, we sought

- A patient or patient advocate because it was important to represent the perspective of older patients who have received care for pain in a variety of healthcare settings and who could inform on what interventions would have been most helpful for them to manage their pain and opioid use.
- A practicing geriatrician since geriatrics healthcare professionals are frequently responsible for managing pain in older adults.
- A pharmacist specializing in geriatrics because pharmacists often lead clinical and quality improvement efforts to manage opioids in older adults as a member of the patient's care team.
- A pain and addiction medicine expert because they, like geriatrics healthcare professionals, are often responsible for managing opioids in older adults but have orthogonal expertise to clinicians with geriatrics expertise.
- A pain medicine specialist practicing in an outpatient or community setting because we anticipated that interventions may be particular important in outpatient settings and we expected that outpatient patient specialists would have unique insights about how pain differs among older adults and how such differences might be risk factors for opioid-related harms, as well as how such differences could be exploited to develop future interventions for older adults.

- A state-level health policymaker or policy advisor because that perspective was thought to be essential to understand risk factors and possible interventions to manage opioid use in older adults at the population level.
- An expert in psychiatry because pain, mental health, and opioid use (and misuse) are strongly related, and psychiatry healthcare professionals have often led efforts to prevent and treat opioid misuse and addiction.
- A non-pharmacist (because pharmacists were explicitly sought) allied (non-physician) healthcare professional or who had expertise in alternative medicine expertise because such individuals, including nurses, chiropractors, and acupuncturists, often manage a large portion of the routine care for older adults with pain, and were expected to have unique perspectives about risk factors as well as interventions that could be implemented by allied healthcare professionals.
- An expert in psychology because the transition from appropriate opioid use to misuse or OUD among older adults may be strongly related to behavior, and since many potential non-pharmacological interventions to intervene on opioid use may arise from the field of psychology, this perspective was viewed as essential.

Key Informant Discussions

We solicited the panel's input in three teleconferences and over email until we deemed that we had sufficiently discussed all of the most relevant themes. The interactions with the Key Informant Panel were facilitated by the Brown EPC and included several structured questions about the Guiding Questions. The Key informants were also asked about the draft Conceptual Framework and to identify peer-reviewed publications or other relevant literature related to the topics of interest. All teleconferences were audio-recorded and transcribed by a member of the EPC team.

All Key Informants were provided with an equal opportunity to speak and all were encouraged to provide input to ensure that no single perspective was over-represented or dominated the discussions.

Based on input and feedback from the Key Informants during discussions, we refined the study eligibility criteria and data extraction items for the evidence map (see section *Evidence Map* below). To summarize the information collected during the Key Informant discussions, we used a combination of notes and transcripts created from audio recordings to map the concepts and themes identified by the Key Informants to the draft conceptual framework. We employed a Systems Mapping (i.e., "Systems Framework") approach to perform the mapping, which involved identifying what care management or other behaviors the Key Informants were speaking about, who was performing those behaviors from the perspective of the Key Informants, and how the behaviors fit within the complex "system" that exists to prevent, diagnosis, and manage opioids, opioid use, and OUD in older adults.[27, 28] The Systems Framework approach to coding the Key Informant discussions was selected because it emphasizes identifying opportunities for change and designing future interventions to targeted specified behaviors.[27]

For a given concept or theme spoken about by the Key Informants, we first identified which person or organization the Key Informant was referring to. In a Systems Framework, this would be the "Actor". We then identified actions that could be directly or indirectly observed. These actions are performed by the actors and referred to as "Behaviors" in the Systems Framework. Finally, we identified circumstances and factors that affected whether a behavior was likely to

happen, which often involved elements of capability, opportunity, and motivation. These circumstances and factors are "Influences" in the Systems Framework. We attempted to maintain the statements made by Key Informants in as close to an original form as possible so as to avoid altering the meaning intended by the Key Informant.

In addition to identifying themes, we focused on which parts of the conceptual framework were spoken about most and least by the Key Informants, and what research Key Informants identified as being most or least urgent and of greatest or least interest.

Further Development of Framework

We iteratively added to and revised our draft framework through discussions with Key Informant panel members. Key Informants also gave input to guide the search process for literature to inform the framework. With each iteration, we used the updated framework to search for new domains, concepts, and factors. These were incorporated into the framework to develop a next iteration. We also continued to search for potentially relevant existing conceptual frameworks and systems maps. During development, we also considered frameworks and systems maps created for older adults with conditions other than pain or opioid use to ensure no relevant concepts are omitted.

Finalization of Framework

The framework was considered final when (1) no new domains, concepts, or factors arose from discussions with the Key Informant panel members and (2) new items offered only small incremental gains in information over previously encoded items because they were primarily derivatives of existing concepts or factors. Informational redundancy between the Key Informant input and conceptual framework figure thus was a key measure of progress toward finalization.

Evidence Map

We conducted a literature search to find articles primarily addressing Guiding Questions 2 and 3 (pertaining to predictors of harms from opioids in older adults and interventions to appropriately reduce opioid prescription, to reduce risk of harms, to identify misuse and OUD, and to treat misuse and OUD in older adults). The literature search and abstract screening processes are described below under *Literature Search Strategies for Identification of Relevant Articles*. We then created a preliminary evidence map from full-text articles. The evidence map enumerates the number of primary studies (along with systematic reviews and clinical practice guidelines) that directly address relevant questions pertaining to the management of opioid use and misuse in older adults. It describes the characteristics of these studies (e.g., their design, basic population descriptors, interventions). It does not summarize the quantitative findings of the studies, nor does it assess either the quality of the studies or the strength of the evidence. The methods for conducting the evidence map are described below, under *Data Extraction and Data Management*.

Evidence Map Eligibility Criteria

Eligible Populations

- Older adults with or without pain prescribed or otherwise using (or having used) opioids (or for whom opioid prescription/use may be warranted)
    - For abstract screening, we used an age threshold of mean or median age ≥50 years. For the evidence map (full-text screening), we used a mean or median age threshold ≥60 years (or analysis of a subgroup ≥60 years within the study)
        - During abstract screening we also included studies of the Veterans Health Administration (and databases) or that used Medicare databases, regardless of age data in the abstract (unless the study was clearly focused on adults <50 years old)
        - During abstract screening we also included studies of surgical or health conditions that primarily affect older adults (e.g., hip arthroplasty, coronary artery bypass, prostate cancer; unless the study was clearly focused on adults <50 years old)
        - During abstract screening we also tagged, but *excluded* large (N>5000) population-based studies that did not explicitly report on an older adult subgroup in their abstracts because they may report sub-analyses of older adults in the full-text article
- Other criteria, applied during both abstract screening and full-text review, included:
    - Any timeframe of opioid use in relation to pain (whether past, present, or none)
    - Any cause of pain (including acute, subacute, chronic, neuropathic, somatic; any severity), including no pain
    - Any use of opioids, whether prescribed or not, legally obtained or not
        - *Exclude* nonopioids use, misuse, or use disorder (e.g., benzodiazepines, anesthetic narcotics) without concomitant use of opioids
    - Study conducted in high-income countries (as defined by the World Bank (https://data.worldbank.org/income-level/high-income)
    - *Exclude* terminally ill, those in hospice care, or others in whom opioid misuse, harms, or OUD are of little concern

Eligible Interventions and Predictors

- Any intervention to predict or manage opioid use, including:
    - Screening questionnaires
    - Prediction tools
    - Clinical decision support tools
    - Quality improvement initiatives / implementation strategies to promote evidence-based care
    - Models of care
    - Other related interventions
- Opioid prescriptions to manage pain
    - Nonopioid medications and non-pharmacologic treatments for pain control (as a comparator)
- Interventions to prevent opioid harms, misuse, or OUD
    - Pharmacologic or non-pharmacologic

- Any predictor (or risk factor or associated variable) of opioid use, misuse, harm, or OUD, including:
    - Patient demographic features (e.g., age, race/ethnicity, sex)
    - Patient social conditions (e.g., housing status, social contacts, employment)
    - Patient setting (e.g., outpatient, inpatient, long-term care)
    - Patient morbidities (e.g., cause of pain, other clinical conditions)
    - Patient cognitive function, quality of life, function
    - Patient history of pain, history of opioid use and misuse
    - Clinic and clinician descriptors (e.g., primary vs. specialty care, specific specialty)
    - Clinical team members (e.g., physician only, nurse outreach, home health aide, pain clinic)

Eligible Outcomes

- Person-level
    - clinical outcomes (e.g., death, falls, cognitive function, cardiovascular events, respiratory function)
    - clinical resources (e.g., ED visits, clinic visits, hospitalizations)
    - living status (e.g., residence, work, activities of daily living, social function)
    - quality of life or function (however measured)
    - pain and pain control
    - opioid use (including long-term use, appropriate dose reduction), misuse, and OUD
    - opioid-related adverse events
- Provider-level outcomes, including but not limited to:
    - barriers/facilitators to/of appropriate opioid prescription
    - provider knowledge
    - attitudes and beliefs
- System-level outcomes, including but not limited to:
    - likelihood of provider adherence to interventions
    - changes in the proportion of providers prescribing opioids appropriately

Eligible Study Designs

- Any primary study design, including
    - Randomized and nonrandomized comparative studies (including intervention comparisons of interest from registry, database, or other cohort studies)
    - Single-group studies (including registry, database, or other cohort studies)
    - Case control studies
    - N-of-1 studies
    - Prospective or retrospective studies
    - Cross-sectional or longitudinal studies
    - Surveys or qualitative research analyses
    - Data reports (e.g., from FDA or pharmacopeia)
- For the question of associations between risk factors and outcomes, in the first screening phase, we included any study design. For final inclusion, we included only studies with multivariable analyses

- Systematic review
- Clinical practice guideline (whether or not evidence-based)
- For the Conceptual Framework, we also tagged narrative articles of potential interest including narrative reviews, editorials, opinion pieces, comments, letters, etc.
- Any timing
- Any setting (in high-income countries)
- English language publication

Rationale for Evidence Map Eligibility Criteria

Eligible Populations

Eligible populations are older adults who use, or may use, opioids for pain management or recreational purposes. Although ≥60 or ≥65 years of age are more traditional age thresholds for identifying older adults, for our preliminary screen of the evidence base we populations as young as 50 years of age for two reasons. First, many studies of opioid misuse and opioid use disorder deviate from traditional age cutoffs and consider individuals aged 50 years or older to be "older adults." Second, the lower age threshold could allow researchers to understand how predictors of opioid use and how opioid use itself changes as individuals transition from middle age to older age.

However, since a primary purpose of this Technical Brief is to inform policymakers in the Centers for Medicare & Medicaid Services (CMS), we focused the evidence map on the population of adults age 65 years or older. Furthermore, fully reviewing studies of populations younger than 65 years would more than double the evidence base, which would not have allowed a feasible review given time and resource constraints for this Technical Brief.

Studies of younger patients and large population-based studies are enumerated briefly. Lists of these studies are available from the Brown EPC.

Eligible Interventions and Predictors

The evidence map aimed to describe all available interventions, both those developed for a younger or general population that have been adapted for older adults and those that were specifically designed for older adults. We were inclusive, in terms of interventions and predictors so that we could describe what has been studied (and what there may be evidence for). Therefore, all interventions and predictors were eligible.

Eligible Outcomes

The Technical Brief aimed to identify what outcomes should (and could) be captured specifically for older adults. Therefore, all patient-level and system-level outcomes were eligible for the evidence map.

Eligible Study Designs

We included all primary study designs along with systematic reviews and clinical practice guidelines.

For the question of predictors of outcomes, we sought to capture independent factors that are most likely to be true predictors. Thus, we limited to multivariable analyses.

Literature Search Strategies for Identification of Relevant Articles

The literature searches were designed to capture articles of interest to support the Conceptual Framework and to be included in the evidence map.

We searched PubMed, PsycINFO, and CINAHL using terms related to older age or aging, crossed with terms on opioid use, opioid-related disorders, opioid misuse, and opioid-related adverse events. We did not include search terms for (and thus avoided excluding articles based on) interventions, outcomes, or study designs. We limited results to studies published in English, between the years 2000 and 2019, inclusive. The rationale underlying the date limits was that opioid prescribing for pain, as it currently occurs in modern clinical practice, began in the 1990s, which is also when opioid prescribing rates dramatically accelerated.

To screen the evidence base, we used the online software Abstrackr, which uses machine learning algorithms to predict and sort citations based on likely relevance. We trained the team in the study eligibility criteria by going through several training cycles where all team members screened the same citations and reconciled conflicts as a group. The training cycles were performed until all screeners were uniform in their assessments. After that pilot phase, citations were double-screened by two reviewers. Based on our experience with the software (and soon-to-be-completed empirical research), we stopped screening citations when the software predicts that no further (unscreened) abstracts are likely to be relevant. We also searched ClinicalTrials.gov and PROSPERO to identify unpublished studies, ongoing studies, and unpublished systematic reviews. We did not record reasons for exclusion at the abstract level.

All potentially eligible citations were retrieved and screened in full text for eligibility. Full text articles were evaluated for eligibility by a single reviewer, after a training period to ensure consistency between all reviewers. For all papers reviewed in full-text we recorded reasons for exclusion.

Data Extraction and Data Management

The evidence map includes a structured set of elements on the population, the intervention (or predictors), examined outcomes, and study design features (PICOD). The evidence map is restricted to primary studies, systematic reviews, and clinical practice guidelines.

- For **populations**, we recorded information on participants age (mean age and whether the study, or an analyzed subgroup, focused on participants ≥60 years, ≥65 years, and/or ≥75 years), special populations (e.g., Medicare, Veterans Administration databases), sex, and race/ethnicity. We captured information on setting (e.g., inpatient, ED, outpatient), how/why opioids were used (e.g., appropriate by prescription, misuse, illicit), and features of people's pain, as relevant, including time course (acute, subacute, chronic) and cause (e.g., surgery, cancer, neuropathic).
- Pertaining to Guiding Question 2, we captured **predictors** (and risk factors) listed in the Guiding Question, including patient demographics, social conditions, setting or environmental factors, pain conditions or comorbidities, cognitive or physical function, frailty or geriatric syndromes, history of pain, history of opioid use or misuse, history of nonopioid substance use disorders, medication factors (e.g., dose) and polypharmacy. We also captured physician characteristics (e.g., primary vs. specialty care), clinical team characteristics, and health system characteristics. Finally, we captured other predictors of potential interest.
- Pertaining to Guiding Question 3, we captured **interventions** listed in the Guiding Question, including screening tools and questionnaires, prediction tools or models,

clinical support tools, quality improvement initiatives or implementation strategies, and models of care. We included opioid and nonopioid medications for pain management, pharmacologic treatments for opioid misuse or OUD (i.e., medication assisted treatments), and non-pharmacologic interventions for opioid misuse or OUD (e.g., cognitive behavioral therapy). Finally, we captured other interventions of potential interest.

- Also pertaining to Guiding Question 3, we extracted information on the **intent of the interventions**, including appropriately reducing opioid use, reducing opioid risks (related to harms, misuse, and OUD), identifying opioid misuse and OUD, treatment of opioid misuse or OUD, to help providers in some other way to management opioid use, and other intents of potential interest.
- We extracted all eligible specific **outcome** categories, including pain, opioid use, opioid prescriptions, "direct" opioid harms (e.g., misuse, OUD, long-term use), "indirect" opioid harms (e.g., falls, cognitive decline, cardiovascular events), physical functioning, emotional functioning (including quality of life), and health service and care utilization. Finally, we captured other outcomes of potential interest.
- We extracted a range of features related to **study design**, including the basic study design (e.g., randomized controlled trial, case series), the directionality (prospective vs. retrospective), and the temporality (cross-sectional vs. longitudinal). We also captured the study's country and setting (e.g., ED), the sample size, enrollment years, and follow-up duration (as relevant).

From each eligible article we extracted bibliographic information (first author, journal, year of publication) and study name (as applicable). All data was extracted in a predefined electronic form.

Assessment of Methodological Risk of Bias of Individual Studies

Technical Briefs do not assess strength of evidence; therefore studies were not assessed for methodological risk of bias.

Data Synthesis

We summarized Key Informant input and use it to inform the design of the Conceptual Framework, in terms of the data items to be extracted; to identify important evidence gaps; and to prioritize gaps into research needs.

To synthesize the evidence base, we first categorized studies as pertaining to either predictor analyses or to identifiable interventions. An individual article could contain both predictor analyses and intervention analyses.

Predictor Studies

Predictor studies are those that describe an association between a predictor and an outcome. The predictors could be characteristics of participants, providers, settings, or regions, such as, respectively, race/ethnicity, provider specialty, clinic type, or poverty level in a given county. For our first-pass inclusion of studies in this category, we did not consider the type of analysis done (e.g., descriptive/narrative only, other qualitative, subgroup data, comparisons of subgroups, regression analyses).

To focus on those studies of greatest potential value to inform either clinical decisionmaking or research into future potential tools or instruments, we focused on those studies that reported multivariable analyses of outcomes of interest within clearly specified cohorts of older adults. From these studies, we extracted data from the reported multivariable analyses, including outcome, predictor and comparator, (adjusted) relative effect size and associated data, and notes as necessary.

When articles reported separate multivariable analyses for different outcomes, these were each extracted separately and in full. When articles reported related or overlapping multivariable analyses of the same outcome (e.g., separate analyses in different subgroups or at different time points), we selected one of the analyses to extract but noted that other analyses were reported. We used our judgment to determine, on a case-by-case basis, which analysis to extract, but erred on the side of including the most complete analysis (e.g., of the total group instead of a subgroup) and/or analyses that provided stronger associations (see next paragraph). Our logic for including the strongest associations was that these studies are providing preliminary assessments of which predictors may accurately predict the outcome in a future instrument to be created and validated. We believe that instrument developers will likely be most interested in, and will further test, all predictors that have been found to be strongly associated with a given outcome.

Within these studies with multivariable analyses, we assigned each reported outcome into a predictor category relevant to the Conceptual Framework. The effect size estimates from these multivariable analyses were each categorized according to the direction of the association and by following schema:

- Strong, *statistically significant* association between (categorical) predictor and higher risk of outcome: relative effect size ≥ 2 (or ≤ 0.5)
- Weak, *statistically significant* association between (categorical) predictor and higher risk of outcome: relative effect size between 0.5 and 2.0
- Statistically significant association between continuous predictor and risk of outcome. Because we could not estimate a standardized effect size, we did not classify these associations as strong or weak.
- No statistically significant association between predictor and outcome (regardless of relative effect size magnitude)

Intervention Studies

We sought those studies that evaluated an identifiable intervention in studies that met eligibility criteria and pertained to older adults. The interventions could be directed at patients, providers, clinics (or other healthcare organizations), or society (e.g., implemented regulations).We describe and summarize these studies within the main report.

Appendix C. Key Informant Discussion

Overview

Here we provide an overview of our discussions with Key Informants that helped to shape the Conceptual Framework and to evaluate the evidence base.

When discussing factors that might potentially be drivers behind increases in opioid use and opioid-related hospitalizations or ED visits, the definition of "older" was a key theme. A considerable degree of uncertainty existed about who should be considered an "older" adult. The lack of clarity presents as a barrier to advancing research and knowledge for geriatric patients, and may serve as a facilitator that encourages more opioid prescribing among older adults by allowing providers to ignore the distinctions between younger and older patients. Additionally, few Key Informants felt there was sufficient clarity about how multimorbidity, polypharmacy, frailty, cognitive and physical impairment, and other characteristics common among older adults should be considered when providers are 1) initially prescribing opioids, 2) continuing opioids, and 3) de-prescribing or de-escalating opioids. The opportunity to speak with other physicians and healthcare professionals to create an appropriate individualized pain treatment plan could help providers to overcome this uncertainty. However, the absence of insurer reimbursement or other financial incentives serves as a major barrier to the formation of interdisciplinary pain treatment teams and treatment plan use. Key Informants pointed out that opioids are a path of much less resistance in comparison, and that providers are forced to make prescribing decisions based on the resources available to them. Aside from or due to interactions with the multitude of provider factors, patient characteristics were also discussed as potential drivers of increased opioid use and related harms among older adults. Cancer, history of substance use across the life course, and attitudes toward legal and illegal drug use were all identified as potentially important patient-level risk factors among older adults.

On the topic of interventions for reducing the risk of potentially inappropriate prescribing of opioids among older adults, Key Informants underscored the severe lack of research and resulting knowledge gap about the comparative effectiveness and safety of opioid versus nonopioid (drug and non-drug) interventions. Knowledge was identified as a pre-requisite for development of any interventions since reducing opioid use will likely require increasing use of nonopioid therapies to address patients' pain. Adaptations to nonopioid treatments are likely to also be necessary for older adults (e.g., physical therapy due to prevalent mobility limitations), but such treatments could reduce opioid use, especially if incorporated into a multimodal stepped care pain therapy approach. There was a fair amount of enthusiasm among Key Informants for multimodal stepped care pain therapy, but resource constraints were identified as a major barrier to widespread implementation and continued use among older adults. Finally, Key Informants highlighted the need to create interdisciplinary pain treatment teams as an intervention, and to develop tools and algorithms for providers to apply to their older patients to help with screening and risk stratification for clinical management. Patient characteristics like frailty, cognitive impairment, dementia, disability, and multimorbidity were noted as characteristics that should be explicitly address during the development phase of any interventions (e.g., screening tools).

The Key Informants were specifically asked about risk factors for opioid misuse, abuse, and OUD in older adults; many felt that the strongest risk factor was likely the lack of provider monitoring. Some Key Informants conceptualized the lack of monitoring as inappropriate management of patients on opioids, which they felt was part of a broader issue around absence of adequate healthcare professional training in pain management and interventions to stimulate

greater uptake of such training. The lack of screening tools specifically designed for or studied in older adults was thought to be a major determinant of misuse, abuse, and OUD. Provider perceptions that older adults are not at significant risk was hypothesized both as a reason for the lack of screening tools in older adults and the reason that opioid misuse, abuse, and OUD may be increasing in this population. Key Informants stated that even when providers believe there is indeed a significant risk, health systems, organizations, and clinical practice settings often do not share their belief or feel that the population at risk is not sufficiently large to merit a focus (i.e., to merit older adult-specific screening tools). Finally, risk factors for opioid misuse, abuse, and OUD in older adults were perceived as empirically unsupported by the data. The absence of data was itself perceived as a risk factor because such information is necessary to develop tools and interventions. This is especially true given that older adults who misuse opioids are hypothesized to differ in their demographic, clinical, and other characteristics from 1) older adults with pain who do not misuse opioids or develop OUD, and 2) younger adults misusing opioids or who have OUD. Opioid contracts were mentioned by Key Informants, but appear not to be widely used for older adults.

When specifically asked about interventions to reduce opioid misuse, abuse, and OUD in older adults, Key Informants were enthusiastic about Screening, Brief Intervention, and Referral to Treatment (SBIRT) and deprescribing protocols. Deprescribing protocols specifically for opioids or focused on pain in older adults do not yet exist per Key Informants, but many felt that they could be effective if they included an appropriate transition to treatments that prevent relapse when the patient is addicted to opioids. There was also enthusiasm for the ORT, which has gained traction among providers due to its brevity and ease of use. While the absence of screening tools was a major theme during discussions of risk factors for opioid misuse, abuse, and OUD in older adults, there was discordance between Key Informants about how to address that issue. Some Key Informants strongly believed that screening tools developed in younger populations could be readily applied to older adults. Others believed that research would be necessary to adapt, validate, and confirm the effectiveness of those tools, especially if OUD prevention was a focus of them. Other Key Informants believed that it would be best to develop new screening tools for older adults that would explicitly take into account older adults' unique demographic and clinical characteristics. Regardless of how tools might ultimately be developed, Key Informants agreed that the feasibility of implementing any tools or interventions is a major concern given health systems' perceived unwillingness to deploy them, allocate sufficient time to providers to apply tools, or train staff.

Many Key Informants believed that co-prescribing of medications with related therapeutic effects, such as benzodiazepines or non-benzodiazepine hypnotics, was the strongest risk factor for opioid-related hospitalizations or ED visits among older adults. Related to co-prescribing, providers unknowingly duplicating another provider's opioid prescription for an older patient (e.g., due to lack of communication) was identified as a major problem and risk factor for opioid-related harm. Providers' inability to accurately assess an older adult's likelihood of benefit from an opioid relative to their likelihood of harm was considered another particularly strong risk. Other risk factors that emerged through Key Informant discussions included polypharmacy, multimorbidity, isolation (e.g., living at home alone), location of residence (e.g., at home versus in a long-term care facility, in a certain state or region), psychiatric conditions (including depression and suicidal ideation), and caregiver support (e.g., the availability of family members to assist with medication management and activities of daily living).

Few interventions were specifically identified to reduce the risk of opioid-related hospitalizations and ED visits among older adults. Key Informants identified the lack of a detailed understanding about why hospitalizations and ED visits related to opioids were increasing over time as a major barrier to developing interventions. No Key Informant was confident in a given explanation or believed the mechanism for the observed time trends was obvious. Interventions involving the training of healthcare professionals and organizing providers into multidisciplinary teams was a repeated focus.

Throughout all discussions, Key Informants identified several areas in which research is urgent and would be particularly impactful:

- Establishing clear age thresholds and distinguishing how risk factors for opioid-related harms vary both within and between age groups
- Distinguishing between age and birth cohort effects as explanations for the increases in opioid-related hospitalizations and ED visits over time
- Comparative effectiveness of opioid versus nonopioid interventions with an explicit focus on frailty, multimorbidity, and other characteristics unique to older adults
- How to clearly define provider responsibilities for prescribing, continuing, and deprescribing opioids when multiple providers care for a single older patient
- Medication and recreational cannabis or marijuana use as both a risk factor for opioid-related harms and a potential intervention to reduce them
- Validation of existing screening tools for opioid misuse or opioid in older adults
- Developing separate screening tools for identifying opioid misuse versus opioid-related harms that occur under appropriate use circumstances or use as prescribed by a provider
- Tramadol use in older adults and how tramadol should fit into a pain management strategy
- How opioids are currently used in older adults with cancer and how pain management can be improved in that population

Table C-1. Systems framework for factors driving opioid use among older adults

Relevant Components	Factor: Actor	Factor: Behavior	Factor: Influences
Patient; Provider; Setting	Provider	Categorization of patients as "older" based on different thresholds of age and applying geriatric prescribing principles heterogeneously based on the threshold selected by one provider versus another	Disagreement between policies and programs (e.g., Older Americans Act versus Medicare health insurance program eligibility) on who should be defined as "older" Clinical guidelines referring to different groups as "older" Researchers defining different groups as "older" (e.g., age ≥50 versus ≥60 versus ≥65)
Patient	Patient	Use of many legal prescription drugs and illegal recreational drugs across the life course in certain age cohorts	Historical and cultural access and acceptance of legal and illegal drug use among present older adult cohort (i.e., "baby boomer" cohort) increases acceptability of taking opioids
Patient; Provider	Provider	Practice trends toward and greater acceptability of using short-acting opioids, lower doses, and opioid products without acetaminophen rather than long-acting opioids in older adults with chronic pain	Provider perception that age (younger vs. older) does not seem to impact use of opioids in chronic pain patients, though providers aim to use more nonopioid treatments in older adults Social and societal expectation to use more nonopioid modalities
Provider, Pain	Provider	Appropriate use of opioids to manage pain (i.e., good pain management care)	Legitimate patient pain requiring opioid management
Provider; Setting	Provider	Inappropriate prescribing and over-prescribing of opioids	Faster and easier to prescribe an opioid than not prescribing a drug or recommending a non-pharmacologic therapy Lack of insurer reimbursement for interdisciplinary communication between providers and development of an opioid-sparing treatment plan
Provider	Provider	Inability to prescribe topical treatments, especially topical nonsteroidal anti-inflammatory drugs (NSAIDs)	Lack of insurer reimbursement for topical NSAIDs and other nonopioid therapies Health system leadership pressure to prescribe opioids and other treatments reimbursed by insurer
Patient; Provider	Provider	Prescribing high-dose or more opioids to an older adult because they have cancer without a thorough assessment of the exact source or type of pain	Patient: cancer Provider perception that cancer pain is a special pain type for which typical pain management and opioid prescribing principles do not apply Provider perception that cancer is broadly a proxy for limited life expectancy (perceived prognosis drives prescribing) Provider conceptualization of cancer as either an acute or chronic condition Provider not assessing source of "cancer pain"—surgical, trauma, chronic, musculoskeletal, neuropathic, etc.

Table C-2. Systems framework for interventions that exist or could exist to reduce the risk of potentially inappropriate prescribing for older adults

Intervention	Relevant Components	Factor: Actor	Factor: Behavior	Factor: Influences
1: Use of nonopioid non-drug alternatives or complementary integrative health (e.g., massage, cognitive behavioral therapy, yoga, acupuncture)	Provider; Guidance	Providers	Inability to recommend nonopioid alternatives credibly or provide such alternatives	Lack of empirical evidence to support the use of many nonopioid treatments (either versus no treatment or opioids) despite the fact that patients seek them out Professional organizations and guideline-creating entities
	Provider; Patient	Provider; Patient	Adapting exercise, cognitive behavioral therapy, physical therapy, and chiropractic interventions to the abilities and unique conditions of older adults	Provider: need to know how to work with older adults and how to adapt intervention (e.g., stretching, flexibility, or strengthening exercises) so that patients can engage despite frailty, cognitive impairment, disability, and other characteristics Patient: Frailty, dementia, and other characteristics, thus interventions need to be adapted; equity factors (some population more likely to have coverage than others) Insurer reimbursement Health system commitment to providing services (e.g., via an Integrative Health Center) despite no or poor reimbursement
2: Use of multimodal stepped care pain therapy to reduce opioid use (i.e., systematically working through nonopioid alternatives)	Provider	Provider (physician; pharmacist; nurse)	Provision of multimodal stepped care pain therapy	Local resources impeding widespread and consistent implementation even when empirical evidence is generated to support the use of multimodal stepped care pain therapy Insurer reimbursement for nonopioid non-drug alternatives

Intervention	Relevant Components	Factor: Actor	Factor: Behavior	Factor: Influences
3: Coordination of care among providers (esp. with mental health)	Provider	Provider	Coordination of mental health, behavioral health, and other providers for older patients with chronic pain	Lack of perceived need for team-based care relative to other acute and chronic clinical conditions. Provider or personnel preparation Failure by providers to use or integrate the resources and skills of other disciplines like counseling, rehabilitation, and mental health Improved coordination of mental health with respect to chronic pain, and lack of clarity about who is responsible for coordination Improved training in other disciplines (e.g., counseling, rehabilitation and mental health), and increased capacity for training Patient: depression
4: Use of interdisciplinary pain programs	Provider	Providers (various, as part of a team; e.g., physical therapy, mental health)	Provision of team-coordinated care from different specialties	Resources impeding implementation, including difficulties obtaining financial support to organize neurosurgeons, physical therapists, pain specialists, geriatricians and others into a team to identify the source(s) of pain and develop a personalized treatment plan Interdisciplinary pain programs and clinics (originally created for complex patient cases) closing over time (since the 1990's), especially in rural areas
	Provider	Providers	Recommendation by physicians or other providers for patient to receive services from acupuncturists, massage therapists, and other non-physician practitioners participating in a patient's care team	Lack of consistency in training and quality control for many disciplines offering nonopioid services, such as massage therapy and acupuncture

Intervention	Relevant Components	Factor: Actor	Factor: Behavior	Factor: Influences
5: Use of diagnostic (and treatment) algorithms, especially for healthcare professionals who are not pain specialists (e.g. many clinicians in primary care)	Provider	Provider	Using diagnosis algorithms for identifying pain and treatment algorithms for managing it with nonopioid therapies	Existence of algorithms adapted to older population, specifically taking into account prevalent contraindications to nonopioid drugs (e.g., declining renal function and the use of either NSAIDs or gabapentin) Existing clinical guidance is not easily operationalized among older adults
6: Risk stratification tools that generate a risk profile for clinicians to use when managing pain and prescribing for older adults	Provider; Setting	Provider	Development of an automated algorithm in older adults that uses a given individual's clinical data as an input and creates a risk profile for likelihood of future benefit, harm, and misuse of opioids	Lack of empirically documented risk factors for opioid misuse in an older population, especially "early life" factors like smoking, childhood trauma, and family history of alcohol or other substance use Incomplete understanding of whether tools must be developed separately for older adults with versus without a history of substance use in order for the tools to have good performance

Table C-3. Systems framework for strongest predictors for opioid misuse, abuse, and opioid use disorder in older adults

Relevant Components	Factor: Actor	Factor: Behavior	Factor: Influences
Provider	Providers, patient	Inappropriate management of people on opioids (and continuation of opioids)	Provider: Futility influenced by lack of training in pain management; lack of familiarity with Food and Drug Administration-approved treatments for opioid use disorder; clinician engagement Patient: stoicism; lower tolerance among older patients for same doses of opioids in younger patients
Provider	Providers (Prescribers)	Prescribing opioids long-term for musculoskeletal conditions causing chronic pain	Unclear/Not specified
Patient	Patient	Addiction to alcohol and concurrent use of alcohol with opioids	Interaction or interplay between birth cohort, age, and nonopioid substance use

Relevant Components	Factor: Actor	Factor: Behavior	Factor: Influences
Provider; Patient; [System]	Provider; System	Lack of care coordination with other providers of patient (e.g., communicate what is being prescribed in one setting to provider in another setting), and therapeutic duplication of another provider's opioid prescription due to ignorance of the other prescription	Patient: multiple conditions leading to care by multiple providers; ability to receive care in multiple systems paid for by multiple insurers (e.g., single patient receiving care from the Veterans Health Administration [VHA] and a non-VHA provider who bill services to Medicare) Provider/Setting: Lack of clarity about what person or entity is responsible for coordinating multiple providers
Provider	Provider	Non-use of opioid contracts	Patient: Age >75 Provider: Greater concern about children or adult caregivers diverting opioids from the older patient and using them
Provider	Provider	Lack of patient referral to behavior health providers who are able to spend more time investigating and assessing for possible opioid misuse	Patient: Age >75 Provider: Greater concern about children or adult caregivers diverting opioids from the older patient and using them
Guidance; Provider	Provider	Lack of using screening tool(s)	Availability (lack) of a tool specific to older adults to predict individual patients' risk of opioid misuse or OUD Availability of prescription drug monitoring plans and urine toxicology (screens) Belief that a lot of data already exists on how to screen, regardless of age Belief that existing screening tools in younger populations are too lengthy and unable to be adopted in routine clinical practice
Provider	Provider	Lack of screening to detect opioid misuse and OUD	Provider: Biases of the practitioners; prevalent beliefs that older adults do not or are unlikely to misuse opioids or develop OUD Patient: End-of-life or palliative care status

Table C-4. Systems framework for interventions that exist or could exist to reduce opioid-related adverse events, misuse, abuse, or opioid use disorder in older adults

Intervention	Relevant Components	Factor: Actor	Factor: Behavior	Factor: Influences
1: Apply guideline-recommended algorithms for detoxification of patients on opioids, transition to alternative treatments to prevent relapse, and deprescribing	Provider, Guidance	Provider	Act in a guideline-concordant manner by detoxing patients on long-term opioids while also transitioning them to a treatment to prevent relapse and overdose	Provider: Training in the use of medications for OUD and how to appropriately manage opioid withdrawal Guidance: by SAMHSA
	Provider; Guidance	Provider	Use of active deprescribing protocols, and where relevant, offering patient enrollment in formal deprescribing programs for opioids or other co-prescribed drugs (e.g., benzodiazepines or non-benzodiazepine hypnotics) that could increase the risk of opioid-related harms (e.g., falls)	Provider: Understanding that writing a simple schedule of reduced doses is not sufficient for appropriate deprescribing Guidance: Clinic protocol, other Patient: presence of opioids and other drugs (e.g., benzodiazepines)
	Provider; Guidance	Provider	Use of deprescribing protocols for those with an index event, such as a recent fall that resulted in an ED visit, and in settings not traditionally related to pain (e.g., a geriatric falls clinic)	Provider: Understanding that writing a simple schedule of reduced doses is not sufficient for appropriate deprescribing Guidance: Clinic protocol, other Patient: presence of index event (e.g., fall)
	Provider; Guidance	Provider	Collaborating with primary care provider and physical therapy to ensure that treatments are substituted when an opioid is deprescribed	Ability to collaborate with primary care provider or physical therapy Patient's ability to tolerate acetaminophen Availability of massage or acupuncture Pain type Patient comorbidities that may serve as a contraindication, especially to oral NSAIDs

Intervention	Relevant Components	Factor: Actor	Factor: Behavior	Factor: Influences
2: Use screening and treatment tools to identify or predict opioid-related harms	Provider; Guidance	Provider (primarily primary care)	Use of screening tools to identify or predict the risk of opioid-related harms (e.g., falls) under appropriate opioid use circumstances	Provider: Capability to use tool Guidance: Brevity of tool Setting: Many health systems faced with the challenge of maintaining many screening tools in the electronic medical record, thus prefer not to implement screening tools that do not apply to the whole health system
	Provider; Guidance	Provider	Use screening tool for misuse of opioids and OUD, such as the Opioid Risk Tool (ORT) designed for primary care settings	Provider: Perceived opioid misuse (e.g., multiple prescribers, using medication for the wrong purpose) Guidance: (barrier) tools can be very lengthy and difficult to implement in practice; the ORT, while simple and validated, has not been tested in older adults
	Provider; Patient	Provider	Use clinical algorithm to screen patients for eligibility to have deprescribing protocols applied	Patient: Presence of concomitant opioid use and benzodiazepine or non-benzodiazepine hypnotic drugs
3: Offer alternatives to opioids (not necessarily after screening or employing guidelines)	Provider; Pain type	Providers (primary care provider, physical therapist)	Offer patient non-pharmacological treatments or topical treatments, including topical NSAIDS, massage, acupuncture)	Patient: Chronic pain condition requiring pain treatment not contraindicated by comorbidities or conditions; likelihood of adherence if patient is required to visit a practitioner (e.g., a massage therapist) multiple times per week Pain type: If pharmacologic or non-pharmacologic treatment addresses that specific pain mechanism effectively (e.g., neuropathic versus musculoskeletal pain)
4: Deploy Screening, Brief Intervention, and Referral to Treatment (SBIRT)	Provider	Providers	Deliver SBIRT to older adults with OUD or who are at high risk of OUD	Provider: availability of a brief intervention like individual or group therapy Patient: availability of a support network

Intervention	Relevant Components	Factor: Actor	Factor: Behavior	Factor: Influences
5: Prescription Drug Monitoring Programs (PDMPs)	Provider	Provider	Using PDMPs to monitor opioid use in older adults	Provider access to PDMPs Ability of PDMP to integrate with electronic medical record systems used by providers to display information Ability of PDMP to facilitate communication between providers

Abbreviations: CDC = centers for disease control and prevention, ED = emergency department, ORT = opioid risk tool, OUD = opioid use disorder, PDMP = prescription drug monitoring program, SBIRT = screening, brief intervention, and referral to treatment, SAMHSA = substance abuse and mental health services administration.

Table C-5. Systems framework for strongest predictors of opioid related hospitalizations or emergency department visits

Relevant Components	Factor: Actor	Factor: Behavior	Factor: Influences
Patient	Patient	Taking multiple medications (engaging in polypharmacy) that interact, produce similar effects, or lead to confusion about regimens (and result in mistakes)	Multiple conditions (multimorbidity) Multiple prescribers
Patient	Patient	Suicide (intentionally overdosing on opioids)	Isolation, depression, suicidal ideation, psychiatric conditions, lack of family support, and general social-behavioral risk
Patient; Provider	Provider	Potentially inappropriate prescribing of opioids among older adults with depression and suicidal ideation	Provider difficulty recognizing depression in older adults; Lack of coordinated care between primary care and mental health providers
Patient; Provider	Provider	Prescribing high doses of opioids	Presence of poorly controlled chronic obstructive pulmonary disease (COPD) or severe liver disease Caregiver knowledge about adverse effect monitoring
Patient; Setting	Caregiver	Helping manage (monitor and administer) medication in older adults (especially those with cognitive impairment or dementia)	Not specified; implied that caregiver support could help older adults avoid unintentional opioid overdoses
Provider; Patient	Provider (multiple; across different conditions)	Poor communication among providers for same patient resulting in multiple opioid prescriptions or prescriptions for medications that interact with opioids	Patient: multiple chronic comorbidities Electronic medical record and administrative billing systems disconnected and not sharing information (e.g., dual enrollment in Medicare and Veterans Health Administration)
Provider	Provider	Not treating older adults' pain properly, especially when pain is chronic (specific behaviors not made explicit)	Lack of training programs in pain management, and subsequent lack of providers trained to properly treat pain Possible implication that medical schools and other health professional schools not offering sufficient training in pain medicine or related principles

Relevant Components	Factor: Actor	Factor: Behavior	Factor: Influences
Provider	Provider	Failure to conduct a more thorough (or any) risk-benefit assessment of prescribing opioids, continuing opioids, or adjusting dose (to keep as low as possible) in an older patient at each clinical visit (with goal of keeping the patient on the lowest dose necessary)	Not explicitly specified; implication was time pressures and potential lack of knowledge among providers Providers asking older adult how much of an opioid they are taking per day or other unit of time, and asking about any adverse events to opioid
Setting; Patient	Patient	Individuals waiting until they are in a pain crisis to use the ED, and using the ED more frequently for pain care	Patient: Rural (vs. urban) residence, community resources, Medicaid expanded (vs. not expanded) states
Provider	Provider	Prescribing inappropriate or less effective nonopioid drugs to manage pain, ultimately resulting in more opioid use later	Resistance from insurance companies, especially toward pain medicine specialists attempting to avoid using opioids (e.g., by using pregabalin) Insurance coverage for nonopioid pain management (i.e., opioids cheaper and easier)
Provider	Provider	Inappropriate prescribing and management of opioids for older persons	Lack of geriatrics training; inequitable distribution of geriatrics providers by geographic region
Setting	Nursing homes and other long-term care providers; health systems	Providing more post-acute care and long-term care at patients' homes rather than in nursing homes, skilled nursing facilities, or other long-term care settings with staff that have potentially more training in pain management and geriatrics	Workforce, workforce training, family caregiving Patient: Care setting preferences

Abbreviations: COPD = chronic obstructive pulmonary disease, ED: emergency department.

Table C-6. Systems framework interventions that exist or could exist to reduce opioid-related hospitalizations or emergency department visits

Intervention	Relevant components	Factor: Actor	Factor: Behavior	Factor: Influences
1: Train providers in pain medicine	Provider; Guidance	Provider	Providing sufficient training in pain medicine or related principles, including how to prescribe nonopioid therapies and deprescribe opioids.	System issues, structural issues Medical, Nursing, Dental, and Health Professional Schools and Training Program curricula
2: Train caregivers	Patient; Provider	Provider	Teach caregivers (e.g., family members, home health aides) about how to monitor for opioid adverse events and how to intervene if an overdose is occurring (e.g., by using naloxone)	Patient: Cognitive impairment or dementia requiring medication management Lack of coverage for home care services Lack of training for family members or home health aides
3: Promotion of collaborative and coordinated care models	Provider	Provider	Collaborating/coordinating care (specifics unclear)	Unclear
4: Increase uptake of long-standing dosing recommendations for older patients	Provider; Guidance	Provider	Initiate opioids at a geriatric dose rather than the recommended adult non-geriatric dose (e.g., at a half or even a quarter of the non-geriatric dose) and titrate up slowly to ensure that the lowest necessary dose is used and the probability of adverse effects is minimized	Provider awareness of clinical recommendation and dosing specific to older adults

Appendix D. Evidence Map and Other Findings

Evidence Map

The literature search yielded 6244 citations, of which 4153 were screened in duplicate. At this stage of screening, the Abstrackr program predicted that the remaining unscreened abstracts would be highly unlikely to be relevant. Consistent with this, the last approximately 200 citations that were screened yielded no potentially relevant abstracts. Figure D-1 summarizes the literature flow.

Citation screening yielded 536 abstracts of potential interest across Guiding Questions. There were 449 articles retrieved in full text and entered into the evidence map. Of these, 258 articles were rejected as not being relevant to Guiding Questions 2 or 3. The primary reasons for rejection included that the study did not report analyses for populations ≥60 years of age (or ≥50 years), articles did not report on analyses specific to older adults (e.g., they only compared findings in older vs. younger adults, not among older adults), the study did not evaluate opioids, or the study evaluated only opioid effectiveness for pain control. Among these studies, we found 74 studies that focused on adults ≥50 years (but not ≥60 years) or had a mean age between 50 and 60 years. A further 133 were rejected for not being a study of an intervention or a multivariable analysis of the association between risk factors and outcomes of interest. Thus, 57 studies, in 58 articles, are included in the report.

PROSPERO

Our search of the PROSPERO database yielded 310 citations. After screening, we found 24 of potential interest, of which 18 were rejected upon inspection of the full records in PROSPERO. Most were rejected because the records did not indicate a focus or an interest in the subgroup of older adults; six records were rejected because the reviews focus on effect and/or safety of opioid treatments.

Figure D-1. Literature flow

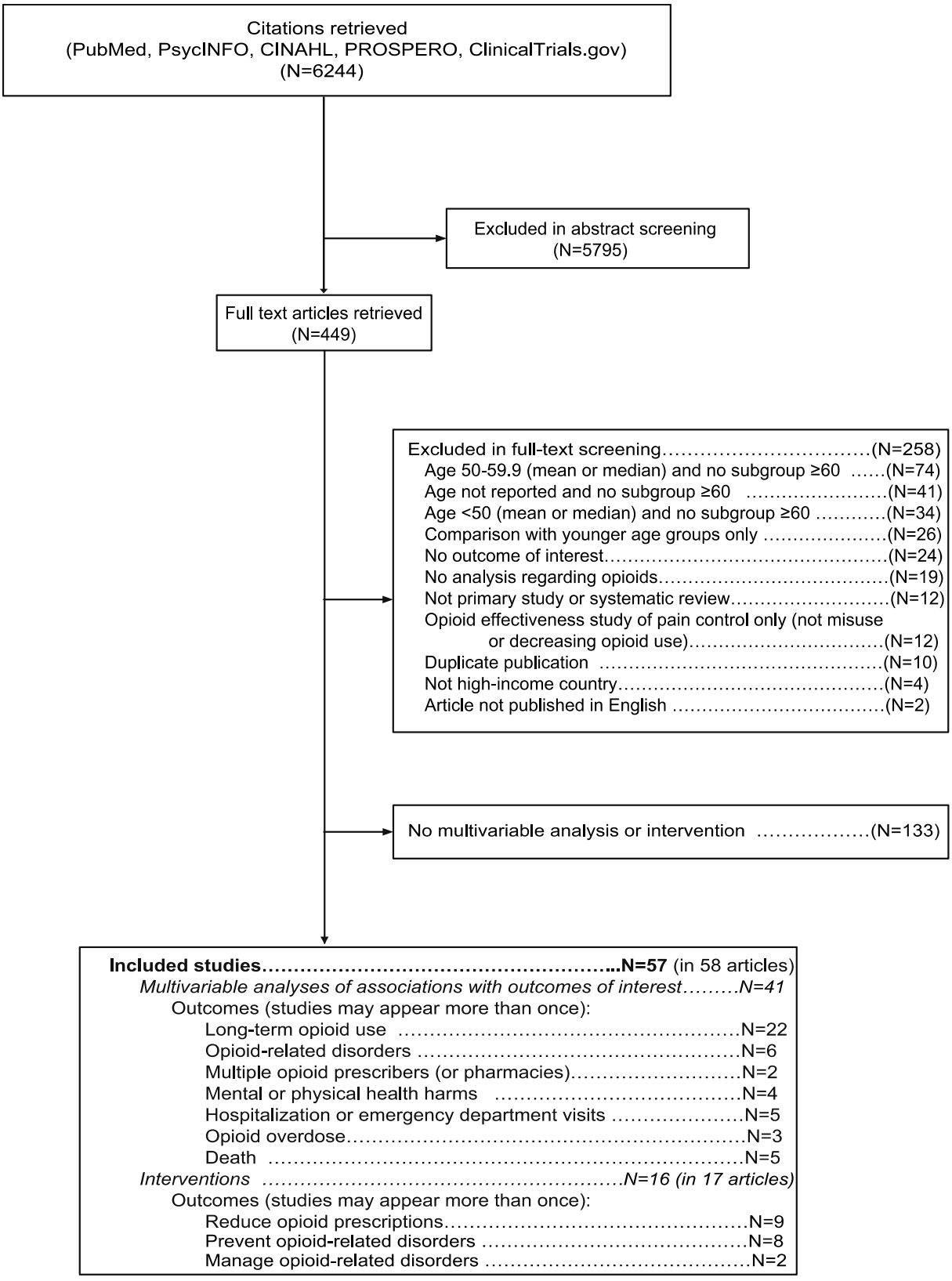

Table D-1. Planned systematic reviews found in PROSPERO

PROSPERO ID	Topic	Condition	Age, Years	Intervention	Outcomes	Study Designs	Search Year	Stage
CRD42018089907	RF for prolonged Tx	Surgery/Trauma	Any (older adult subgroup)	(None)	Prolonged opioid use	Any	2018	Completed, published
CRD42018081577	Screening for opioid use	Chronic non-cancer pain	Any (older adult subgroup)	Opioid consumption assessment tools	Opioid use	Instrument development	2018	Ongoing
CRD42018092943	Screening for opioid harms	Pain	≥65	(None)	Cognitive	Any	2019	Ongoing
CRD42019110462	Treatment of OUD	OUD, etc.	≥50	Opioid agonist therapy	Facilitators, barriers, etc.	Any, including QR	2019	Ongoing
CRD42018105429	Prevalence of OUD	Residents in post-acute care facilities	19+	(None)	OUD etc. (prevalence)	Any	2018	Ongoing
CRD42017057904	Pain assessment	Dementia	Any	Pain assessment techniques	Pain, Tx, QoL, etc.	Any	2017	Completed, not published
CRD42018107045	Experiences with pain Tx	Pain	≥65	(None)	Pain, Fxn, QoL, Experiences	QR	2019	Ongoing

Abbreviations: Fxn = function, ID = identification number, OUD = opioid use disorder, QoL = quality of life, QR = qualitative research, RF = risk factors, Tx = treatment(s).

Table D-2. Ongoing studies in ClinicalTrials.gov

ClinicalTrials.gov Identifier	Status	Study Results	Conditions	Interventions / Exposures	Outcome Measures	Age, Years	Enrollment, N	Study Designs	Completion Date
NCT02090972	Completed	No Results Available	None, per se	Opioid use	Bone density measures	≥60	1000	Case Control	Feb 2015
NCT02691754	Completed	No Results Available	Osteoarthritis	Acetaminophen (free from pharmacy)	Opioid consumption	≥65	16	RCT	Nov 2013

Abbreviation: RCT = randomized controlled trial.

Table D-3a. Studies with multivariable analyses of associations: Outcome data

Rows*	Author Year	PMID	Outcome Category	Outcome
1-3	Al Dabbagh 2016	26707940	Long-term use	Earlier discontinuation of opioid prescriptions
4	Alam 2012	22412106	Long-term use	Long-term opioid Use
5-21	Brescia 2019	31447051	Long-term use	New persistent long term use
22-42	Cancienne 2018	28887020	Long-term use	Prolonged postoperative opioid use after total knee arthroplasty
43-48	Carey 2018	29800019	Overdose	Opioid overdose
49	Carter 2019	30863796	Death	Death (vs. routine ED discharge)
50-60	Carter 2019	30863796	Opioid misuse	Opioid misuse
61-78	Choi 2017	28699829	Opioid misuse	Opioid use disorder
79-86	Choi 2019	30585135	Hospitalization	Any ED visit
87-95	Cochran 2017	28489491	Opioid misuse	Count of symptoms of prescription opioid misuse (via the POMI Prescription Opioid Misuse Index)
96-122	Curtis 2017	28635179	Long-term use	Long-term opioid use (>90 days)
123-140	Daoust 2018	28767563	Long-term use	Opioid use 1 year after injury
141-145	Dasinger 2019	30879796	Hospitalization	Post-discharge readmission within 30 days
146-158	Gold 2016	27564407	Opioid misuse	High-Risk Obtainment of Prescription Opioids
159-168	Grigoras 2018	29159797	Death	Opioid mortality
169-172	Grigoras 2018	29159797	Death	Synthetic opioid mortality
173-176	Grigoras 2018	29159797	Death	Natural and semi-synthetic opioid mortality
177-179	Grigoras 2018	29159797	Death	Heroin mortality
180-182	Grigoras 2018	29159797	Death	Methadone mortality
183-207	Hadlandsmyth 2018	28927564	Long-term use	Opioid Use at 12 Months
208-220	Hamina 2017	28092324	Long-term use	Long-term opioid use
221	Hoffman 2017	28531306	Harm/mental health	Depression
222	Hoffman 2017	28531306	Harm/mental health	Alcohol abuse
223	Hoffman 2017	28531306	Harm/mental health	Other substance abuse
224	Hoffman 2017	28531306	Harm/mental health	Other substance overdose
225	Hoffman 2017	28531306	Harm/mental health	Other substance dependence
226	Hoffman 2017	28531306	Long-term use	Opioid dependence
227	Hoffman 2017	28531306	Opioid misuse	Opioid abuse
228	Hoffman 2017	28531306	Overdose	Opioid overdose
229-246	Inacio 2016	27130165	Long-term use	New chronic opioid use
247-256	Jain 2018	29561298	Long-term use	Long-term opioid use
257-258	Jeffery 2018	28967517	Long-term use	Long-term opioid use
259-262	Jena 2014	24553363	Hospitalization	admission to hospital
263-278	Jena 2014	24553363	Multiple prescribers	prescribing of opioids by multiple providers
279-293	Karttunen 2019	30370943	Long-term use	Prolonged opioid use

Rows*	Author Year	PMID	Outcome Category	Outcome
294-295	Kuo 2016	26522794	Hospitalization	ER visit
296-297	Kuo 2016	26522794	Hospitalization	Hospitalization
298-317	Lalic 2018	29451672	Long-term use	Opioid persistence
318-328	Lindestrand 2015	25952252	Long-term use	Persistent opioid use (6 mo after hip fracture)
329-335	Lo-Ciganic 2019	30901048	Overdose	Opioid overdose
336-339	Loeb 2020	31584849	Long-term use	New chronic opioid use
340-356	McDermott 2019	30396321	Long-term use	Continuous Opioid Use at 6 Months
357-395	Musich 2019	30401575	Long-term use	Chronic opioid use> 90 days
396-442	Namba 2018	29753617	Long-term use	Number of Prescriptions days 271-360 post-op
443-470	Nelson 2020	31445908	Long-term use	Persistent opioid use
471-482	Park 2010	20664342	Opioid misuse	Opioid misuse
483-531	Rao 2018	29891412	Long-term use	Opioid use days 271-360 postoperative
532-573	Santosa 2020	31349994	Long-term use	New persistent opioid use
574-575	Schepis 2019	30328160	Harm/mental health	Suicidal ideation
576-610	Shah 2019	31026356	Long-term use	Prolonged Opioid Prescribing
611-637	Suda 2017	28408172	Multiple prescribers	Opioid overlap (multiple prescribers)
638-645	Taipale 2019	30325873	Harm/physical	Hip fracture
646	Vozoris 2016	27418553	Death	COPD or pneumonia-related mortality
647	Vozoris 2016	27418553	Death	All-cause mortality
648	Vozoris 2016	27418553	Harm/physical	Outpatient respiratory exacerbations
649	Vozoris 2016	27418553	Hospitalization	Emergency room visits for COPD or pneumonia
650	Vozoris 2016	27418553	Hospitalization	Hospitalisations for COPD or pneumonia
651	Vozoris 2016	27418553	Hospitalization	ICU admissions during hospitalisations for COPD or pneumonia
652	Zeng 2019	30860559	Death	All-cause mortality
653-661	Zoorob 2018	29537112	Death	Drug overdose fatality (very high overdose vs low overdose at county-level)

* Row numbers are included to help the reader align the various sections of the table. In this first section, duplicate (identical) rows are condensed and the ranges of relevant rows in other sections of the table are presented.

Table D-3b. Studies with multivariable analyses of associations: Factor data and estimates

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
1	Al Dabbagh 2016	Age	Age ≥70	1.9 (1.5–2.3) < 0.001
2	Al Dabbagh 2016	Gender	Female	1.2 (1.0–1.4) 0.1
3	Al Dabbagh 2016	Cause of pain	Fracture type: Open	0.6 (0.4–1.0) 0.06
4	Alam 2012	Opioid use	Age	1.44 (1.39-1.50)
5	Brescia 2019	Comorbidity	Gastrointestinal complication	1.49 (1.05-2.12) 0.026
6	Brescia 2019	Cause of pain	Open lung resection	1.32 (1.07-1.63) 0.008
7	Brescia 2019	Opioid use	Periop opioid Rx pre-surgery	1.98 (1.74-2.24) <0.001
8	Brescia 2019	Opioid amount	Total perioperative opioid dose, per OME	1.00 (1.00-1.00) <0.001
9	Brescia 2019	Comorbidity	Length of hospital stay, d	1.03 (1.02-1.04) <0.001
10	Brescia 2019	Age	Age, y	0.99 (0.98-1.00) 0.018
11	Brescia 2019	Gender	Female	1.14 (1.04-1.25) 0.007
12	Brescia 2019	Race/ethnicity	Black	1.50 (1.29-1.75) <0.001
13	Brescia 2019	Income	Dual Medicare and Medicaid eligibility	1.40 (1.25-1.57) <0.001
14	Brescia 2019	Comorbidity	Disability (Medicare qualification status)	1.46 (1.23-1.73) <0.001
15	Brescia 2019	Comorbidity	Charlson Comorbidity Index 3,4	1.14 (1.02-1.26) 0.018
16	Brescia 2019	Tobacco	Tobacco use, current or past	1.10 (1.01-1.20) 0.021
17	Brescia 2019	Mental health	Schizophrenia	0.69 (0.52-0.91) 0.010
18	Brescia 2019	Substance misuse	Drug and substance use disorder	1.31 (1.05-1.63) 0.017
19	Brescia 2019	Cause of pain	Arthritis	1.13 (1.04-1.23) 0.006
20	Brescia 2019	Cause of pain	Back pain	1.27 (1.16-1.38) <0.001
21	Brescia 2019	Cause of pain	Other pain disorder	1.10 (1.02-1.19) 0.019
22	Cancienne 2018	Opioid use	Overall (any?) narcotic prescription filled preoperatively	5.47 (5.31-5.64) <0.0001
23	Cancienne 2018	Opioid amount	Filled one narcotic prescription filled preoperatively	2.78 (2.68-2.90) <0.0001
24	Cancienne 2018	Opioid amount	Filled two narcotic prescriptions filled preoperatively	5.93 (5.62-6.26) <0.0001
25	Cancienne 2018	Opioid amount	Filled three narcotic prescriptions filled preoperatively	15.05 (14.00-16.17) <0.0001
26	Cancienne 2018	Opioid amount	Filled four or more narcotic prescriptions filled preoperatively	20.34 (18.69-22.14) <0.0001
27	Cancienne 2018	Opioid use	Tramadol preoperative prescription filled	1.02 (0.98-1.06) 0.394
28	Cancienne 2018	Nonpain tx	Anxiolytics preoperative prescription filled	1.52 (1.46-1.58) <0.0001
29	Cancienne 2018	Nonopioid pain tx	Muscle relaxants preoperative prescription filled	1.64 (1.55-1.74) <0.0001
30	Cancienne 2018	Methadone	Methadone preoperative prescription filled	3.68 (2.90-4.68) <0.0001
31	Cancienne 2018	Tobacco	Tobacco use preoperatively	1.44 (1.39-1.51) <0.0001
32	Cancienne 2018	Substance misuse	Alcohol abuse preoperatively	1.19 (1.10-1.29) <0.0001
33	Cancienne 2018	Substance misuse	Marijuana use/abuse preoperatively	1.47 (1.15-1.89) 0.002
34	Cancienne 2018	Substance misuse	Cocaine use/abuse preoperatively	1.24 (0.85-1.79) 0.263
35	Cancienne 2018	Substance misuse	Amphetamine use/abuse preoperatively	1.14 (0.72-1.82) 0.578
36	Cancienne 2018	Gender	Male	1.03 (1.00-1.07) 0.053
37	Cancienne 2018	Comorbidity	Obesity (BMI 30-39.9)	1.08 (1.04-1.12) <0.0001

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
38	Cancienne 2018	Comorbidity	Morbid obesity (BMI >=40)	1.35 (1.31-1.40) <0.0001
39	Cancienne 2018	Mental health	Depression	1.32 (1.28-1.36) <0.0001
40	Cancienne 2018	Cause of pain	Back pain/lumbago	1.38 (1.34-1.42) <0.0001
41	Cancienne 2018	Cause of pain	Migraine headaches	1.22 (1.16-1.29) <0.0001
42	Cancienne 2018	Cause of pain	Fibromyalgia	1.17 (1.13-1.21) <0.0001
43	Carey 2018	Opioid misuse	>210 days of opioid supplied in 180 days	3.49 (3.22-3.77)
44	Carey 2018	# Prescribers or pharmacists	Any overlapping opioid claim	3.17 (2.96–3.38)
45	Carey 2018	# Prescribers or pharmacists	≥5 prescribers	4.15 (3.78–4.52)
46	Carey 2018	# Prescribers or pharmacists	≥5 pharmacies	5.46 (4.75–6.16)
47	Carey 2018	# Prescribers or pharmacists	Any out-of-state prescriber	2.34 (2.07–2.61)
48	Carey 2018	# Prescribers or pharmacists	Any out-of-state pharmacy	1.77 (1.52–2.02)
49	Carter 2019	Opioid misuse	Opioid misuse	0.85 (0.72, 0.99)
50	Carter 2019	Age	Age 65-74	6.75 (6.63, 7.27)
51	Carter 2019	Age	Age 75–84	2.16 (1.99, 2.34)
52	Carter 2019	Gender	Female	1.12 (1.07, 1.16)
53	Carter 2019	Comorbidity	No. of chronic conditions	1.27 (1.26, 1.28)
54	Carter 2019	Substance misuse	Alcohol-related visit	2.88 (2.70, 3.07)
55	Carter 2019	Cause of pain	Injury-related visit	2.89 (2.77, 3.02)
56	Carter 2019	Insurance	Medicaid	1.56 (1.41, 1.73)
57	Carter 2019	Insurance	Non-Medicaid/Medicare	0.84 (0.79, 0.89)
58	Carter 2019	Income	Income: Lowest quartine	1.26 (1.20, 1.31)
59	Carter 2019	Income	Income: Highest quartine	0.78 (0.74, 0.82)
60	Carter 2019	Residence	Rural residence	0.99 (0.94, 1.04)
61	Choi 2017	Substance misuse	Marijuana use disorder, past year	2.95 (1.11–7.79)
62	Choi 2017	Age	Age, per year (implied)	0.96 (0.94–0.99)
63	Choi 2017	Gender	Male	0.96 (0.58–1.58)
64	Choi 2017	Race/ethnicity	Non-Hispanic Black	1.15 (0.62–2.12)
65	Choi 2017	Race/ethnicity	Hispanic	1.92 (1.08–3.39)
66	Choi 2017	Race/ethnicity	American Indian	2.30 (0.69–7.65)
67	Choi 2017	Social	Married/cohabiting	0.93 (0.60–1.44)
68	Choi 2017	Education	College degree	0.80 (0.41–1.56)
69	Choi 2017	Employment	Employed full-/part-time	0.58 (0.37–0.89)
70	Choi 2017	Comorbidity	Chronic conditions, n	1.12 (0.92–1.36)

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
71	Choi 2017	Cause of pain	Injury, past year	1.51 (0.96–2.38)
72	Choi 2017	Pain	Pain interference: Little/moderate	3.94 (1.73–8.95)
73	Choi 2017	Pain	Pain interference: Severe	9.68 (3.90–24.08)
74	Choi 2017	Mental health	Major depressive disorder, past year	0.96 (0.55–1.66)
75	Choi 2017	Mental health	Anxiety disorder, past year	2.71 (1.56–4.72)
76	Choi 2017	Mental health	PTSD, past year	1.34 (0.69–2.62)
77	Choi 2017	Substance misuse	Alcohol use disorder, past year	2.95 (1.67–5.21)
78	Choi 2017	Tobacco	Nicotine use disorder, past year	1.70 (1.03–2.82)
79	Choi 2019	Opioid use	Opioid use, not misuse	2.25 (2.05–2.47)
80	Choi 2019	Opioid misuse	Opioid misuse	1.99 (1.55–2.56)
81	Choi 2019	Opioid use	Opioid use, not misuse	2.87 (2.48–3.32)
82	Choi 2019	Opioid misuse	Opioid misuse	2.57 (1.88–3.51)
83	Choi 2019	Opioid use	Opioid use, not misuse	1.13 (1.04–1.23)
84	Choi 2019	Opioid misuse	Opioid misuse	1.16 (0.98–1.38)
85	Choi 2019	Opioid use	Opioid use, not misuse	1.32 (1.15–1.50)
86	Choi 2019	Opioid misuse	Opioid misuse	1.05 (0.77–1.42)
87	Cochran 2017	Opioid misuse	Illicit drug use	2.4 (1.46–3.95) 0.001
88	Cochran 2017	Substance misuse	Hazardous drinking	0.91 (0.49–1.69) 0.76
89	Cochran 2017	Mental health	Depression	1.2 (0.80–1.80) 0.37
90	Cochran 2017	Mental health	PTSD	0.86 (0.46–1.61) 0.65
91	Cochran 2017	Comorbidity	General health	1.6 (0.63–4.07) 0.33
92	Cochran 2017	Pain	Pain	1.30 (0.55–3.05) 0.55
93	Cochran 2017	Gender	Female	0.48 (0.13–1.77) 0.27
94	Cochran 2017	Education	Less than high school	0.3 (0.03–2.92) 0.31
95	Cochran 2017	Residence	Rural pharmacy	0.23 (0.04–1.27) 0.09
96	Curtis 2017	Age	Age, 5-year increments	0.83 (0.82–0.83)
97	Curtis 2017	Gender	Male	0.86 (0.84–0.88)
98	Curtis 2017	Race/ethnicity	White Race	0.85 (0.82–0.88)
99	Curtis 2017	Race/ethnicity	Other Race	0.63 (0.59–0.66)
100	Curtis 2017	Comorbidity	Acute myocardial infarction	0.94 (0.90–0.98)
101	Curtis 2017	Comorbidity	Coronary heart disease	1.11 (1.08–1.14)
102	Curtis 2017	Comorbidity	Peripheral vascular disorder	1.18 (1.14–1.22)
103	Curtis 2017	Comorbidity	Cerebrovascular disease	0.89 (0.86–0.93)
104	Curtis 2017	Comorbidity	Chronic pulmonary disease	1.18 (1.15–1.21)
105	Curtis 2017	Comorbidity	Other rheumatic disease (aside from RA)	1.07 (1.03–1.12)
106	Curtis 2017	Comorbidity	Peptic ulcer disease	1.35 (1.25–1.46)
107	Curtis 2017	Comorbidity	Hemiplegia or paraplegia	0.70 (0.61–0.81)

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
108	Curtis 2017	Comorbidity	Renal disease	1.29 (1.25–1.33)
109	Curtis 2017	Comorbidity	Moderate or severe liver disease	1.22 (1.00–1.50)
110	Curtis 2017	Cause of pain	Metastatic solid tumor	1.85 (1.65–2.06)
111	Curtis 2017	Cause of pain	Back pain	2.96 (2.89–3.03)
112	Curtis 2017	Cause of pain	Soft tissue rheumatism including fibromyalgia	1.75 (1.71–1.79)
113	Curtis 2017	Mental health	Anxiety	1.46 (1.42–1.51)
114	Curtis 2017	Mental health	Depression	1.66 (1.61–1.71)
115	Curtis 2017	Nonpain tx	Biologic disease- modifying antirheumatic drug	1.32 (1.29–1.35)
116	Curtis 2017	Nonopioid pain tx	1–2 fills and less than a 90-day supply of NSAID	1.30 (1.26–1.34)
117	Curtis 2017	Nonopioid pain tx	3 or more fills or more than a 90-day supply of NSAID	1.47 (1.44–1.51)
118	Curtis 2017	Healthcare utilization	Any hospitalization	2.31 (2.25–2.38)
119	Curtis 2017	Healthcare utilization	Any claim for durable medical equipment	1.66 (1.63–1.70)
120	Curtis 2017	Income	Median household income Quartile 1	1.46 (1.41–1.51)
121	Curtis 2017	Income	Median household income Quartile 2	1.33 (1.29–1.37)
122	Curtis 2017	Income	Median household income Quartile 3	1.20 (1.17–1.24)
123	Daoust 2018	Gender	Female	1.27 (1.16–1.38)
124	Daoust 2018	Cause of pain	Motor vehicle accident	0.87 (0.75–1.00)
125	Daoust 2018	Cause of pain	Weapon or blunt object	0.98 (0.73–1.31)
126	Daoust 2018	Cause of pain	2 injuries	1.01 (0.92–1.10)
127	Daoust 2018	Cause of pain	>=3 injuries	0.95 (0.85–1.07)
128	Daoust 2018	Cause of pain	Head injury	0.97 (0.84–1.11)
129	Daoust 2018	Cause of pain	Face injury	1.08 (0.95–1.24)
130	Daoust 2018	Cause of pain	Thorax injury	1.15 (1.03–1.28)
131	Daoust 2018	Cause of pain	Spine injury	1.62 (1.46–1.80)
132	Daoust 2018	Cause of pain	Lower extremity	1.32 (1.13–1.53)
133	Daoust 2018	Cause of pain	Major trauma (ISS >15)	0.81 (0.69–0.95)
134	Daoust 2018	Substance misuse	History of alcoholism	1.28 (0.94–1.74)
135	Daoust 2018	Mental health	History of depression	1.32 (1.13–1.53)
136	Daoust 2018	Mental health	History of anxiety	1.12 (0.99–1.27)
137	Daoust 2018	Healthcare utilization	Surgery during hospitalization	0.99 (0.91–1.07)
138	Daoust 2018	Opioid amount	1 opioid prescription in prior 12 months	2.26 (2.00–2.56)
139	Daoust 2018	Opioid amount	>=2 opioid prescriptions in prior 12 mo	11.4 (10.5–12.5)
140	Daoust 2018	Opioid use	Opioid prescriptions w/in 3 mo of trauma	3.05 (2.83–3.29)
141	Dasinger 2019	Opioid use	Preop opioids infrequent	1.17 (1.04-1.31)
142	Dasinger 2019	Opioid use	Preop opioids not daily	1.28 (1.08-1.52)

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
143	Dasinger 2019	Opioid use	Preop opioids daily	1.49 (1.27-1.74)
144	Dasinger 2019	Opioid use	Opioids "on hand" at (first) admission	1.15 (1.00-1.31) <0.05 implied
145	Dasinger 2019	Opioid use	Opioid Rx filled at (first) discharge	1.13 (1.04-1.23)
146	Gold 2016	Opioid misuse	Lifetime recreational use of prescription opioids	3.0 (2.4–3.4)
147	Gold 2016	Age	Age 65-69	2.4 (1.7–2.9)
148	Gold 2016	Age	Age 70-74	1.6 (0.9–2.4)
149	Gold 2016	Age	Age 75-79	2.2 (1.5–2.9)
150	Gold 2016	Age	Age 80-84	2.9 (2.2–3.3)
151	Gold 2016	Age	Age >=85	2.8 (2.0–3.3)
152	Gold 2016	Gender	Female	1.6 (1.2–2.0)
153	Gold 2016	Education	Some college	1.9 (1.4–2.4)
154	Gold 2016	Education	College degree	2.1 (1.5–2.6)
155	Gold 2016	Social	Social connectedness (Lubben Social Network Scale-6; higher more connected)	2.0 (1.8–2.3)
156	Gold 2016	Quality of life	Mental and physical health (SF-12)	1.3 (0.6–2.3)
157	Gold 2016	Opioid misuse	Lifetime illicit drug use	1.8 (1.6–2.1)
158	Gold 2016	Tobacco	Cigarette use in past year	1.5 (0.9–2.4)
159	Grigoras 2018	Income	Under poverty line, % in county	0.28 <0.001
160	Grigoras 2018	Opioid prescription	Prescription rate in county	0.28 <0.001
161	Grigoras 2018	Race/ethnicity	White, % in county	0.16 <0.001
162	Grigoras 2018	Opioid prescription	Physicians, opioid-prescribing, Medicare-enrolled, per county population	-0.07 0.01
163	Grigoras 2018	Specialty	Emergency medicine prescription rate	0.21 <0.001
164	Grigoras 2018	Specialty	Family medicine prescription rate	0.11 0.008
165	Grigoras 2018	Specialty	Internal medicine prescription rate	0.10 0.018
166	Grigoras 2018	Specialty	Physician assistant prescription rate	0.08 0.021
167	Grigoras 2018	Opioid prescription	Super-prescriber prescription rate	0.14 <0.001
168	Grigoras 2018	Opioid prescription	Non-super-prescriber prescription rate	0.07 <0.001
169	Grigoras 2018	Income	Under poverty line, % in county	0.53 <0.001
170	Grigoras 2018	Opioid prescription	Prescription rate in county	0.32 0.02
171	Grigoras 2018	Race/ethnicity	White, % in county	0.41 <0.001
172	Grigoras 2018	Opioid prescription	Physicians, opioid-prescribing, medicare-enrolled, per county population	-0.32 <0.001
173	Grigoras 2018	Income	Under poverty line, % in county	0.37 <0.001
174	Grigoras 2018	Opioid prescription	Prescription rate in county	0.26 0.05
175	Grigoras 2018	Race/ethnicity	White, % in county	0.21 0.001

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
176	Grigoras 2018	Opioid prescription	Physicians, opioid-prescribing, medicare-enrolled, per county population	-0.22 <0.001
177	Grigoras 2018	Income	Under poverty line, % in county	0.42 <0.001
178	Grigoras 2018	Opioid prescription	Prescription rate in county	0.49 0.03
179	Grigoras 2018	Race/ethnicity	White, % in county	0.37 <0.001
180	Grigoras 2018	Income	Under poverty line, % in county	0.33 <0.001
181	Grigoras 2018	Opioid prescription	Prescription rate in county	0.44 0.05
182	Grigoras 2018	Race/ethnicity	White, % in county	0.26 0.007
183	Hadlandsmyth 2018	Gender	Female	0.53 (0.21-1.35)
184	Hadlandsmyth 2018	Age	Age >70	0.935
185	Hadlandsmyth 2018	Race/ethnicity	African American	0.70 (0.38-1.27)
186	Hadlandsmyth 2018	Race/ethnicity	Other race	2.16 (0.91-5.15)
187	Hadlandsmyth 2018	Comorbidity	BMI: Underweight	5.11 (0.52-50.63)
188	Hadlandsmyth 2018	Comorbidity	BMI: Overweight/obese	1.03 (0.42-2.54)
189	Hadlandsmyth 2018	Cause of pain	Pre-TKA chronic pain	1.25 (0.84-1.86)
190	Hadlandsmyth 2018	Comorbidity	Charlson Comorbidity index: 2-3	0.69 (0.43-1.14)
191	Hadlandsmyth 2018	Comorbidity	Charlson Comorbidity index: 4-5	0.82 (0.46-1.48)
192	Hadlandsmyth 2018	Comorbidity	Charlson Comorbidity index: >5	1.26 (0.63-2.48)
193	Hadlandsmyth 2018	Opioid use	Pre-TKA opioid use	7.81 (4.07-15.00)
194	Hadlandsmyth 2018	Mental health	Psychiatric diagnosis	1.04 (0.63-1.71)
195	Hadlandsmyth 2018	Substance misuse	Substance use	1.74 (1.01-2.99)
196	Hadlandsmyth 2018	Nonopioid pain tx	Muscle relaxant use, prior not active	0.67 (0.17-2.69)
197	Hadlandsmyth 2018	Nonopioid pain tx	Muscle relaxant use, active	1.94 (1.28-2.94)
198	Hadlandsmyth 2018	Benzo	Benzo use, prior not active	1.11 (0.26-4.71)
199	Hadlandsmyth 2018	Benzo	Benzo use, active	1.10 (0.69-1.75)
200	Hadlandsmyth 2018	Nonpain tx	Non-benzo hypnotic use, prior not active	0.62 (0.09-4.42)
201	Hadlandsmyth 2018	Nonpain tx	Non-benzo hypnotic use, active	0.83 (0.44-1.58)
202	Hadlandsmyth 2018	Nonpain tx	Antidepressant use, prior not active	0.40 (0.06-2.78)
203	Hadlandsmyth 2018	Nonpain tx	Antidepressant use, active	0.93 (0.56-1.54)
204	Hadlandsmyth 2018	Nonpain tx	Antiepileptic use, prior not active	0.45 (0.06-3.37)
205	Hadlandsmyth 2018	Nonpain tx	Antiepileptic use, active	1.38 (0.90-2.12)
206	Hadlandsmyth 2018	Healthcare utilization	Duration of hospital stay, per day	1.00 (0.99-1.01)
207	Hadlandsmyth 2018	Cause of pain	Unilateral knee replacement	0.19 (0.05-0.76)
208	Hamina 2017	Comorbidity	Alzheimer disease	1.07 (1.02-1.12)
209	Hamina 2017	Gender	Female	1.32 (1.24-1.40)
210	Hamina 2017	Age	Age ≥80	1.20 (1.14-1.27)
211	Hamina 2017	Income	Medium SES	1.01 (0.96-1.07)

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
212	Hamina 2017	Income	Low SES	1.27 (1.16-1.40)
213	Hamina 2017	Comorbidity	Asthma/COPD	1.06 (0.98-1.14)
214	Hamina 2017	Comorbidity	CVD	1.15 (1.09-1.21)
215	Hamina 2017	Comorbidity	DM	1.08 (1.01-1.16)
216	Hamina 2017	Cause of pain	Hx of hip fracture	1.12 (1.01-1.25)
217	Hamina 2017	Cause of pain	Osteoporosis	1.31 (1.23-1.39)
218	Hamina 2017	Cause of pain	Rheumatoid arthritis	1.35 (1.23-1.49)
219	Hamina 2017	Substance misuse	History of substance abuse	1.26 (1.07-1.48)
220	Hamina 2017	Benzo	History of long-term benzodiazepine use	1.62 (1.54-1.71)
221	Hoffman 2017	Opioid duration	Opioid treatment ≥90 days	1.53 (1.29-1.82)
222	Hoffman 2017	Opioid duration	Opioid treatment ≥90 days	1.38 (0.90-2.11)
223	Hoffman 2017	Opioid duration	Opioid treatment ≥90 days	1.81 (0.92-3.58)
224	Hoffman 2017	Opioid duration	Opioid treatment ≥90 days	1.82 (0.92-3.6)
225	Hoffman 2017	Opioid duration	Opioid treatment ≥90 days	1.73 (1.21-2.49)
226	Hoffman 2017	Opioid duration	Opioid treatment ≥90 days	2.85 (1.54-5.47)
227	Hoffman 2017	Opioid duration	Opioid treatment ≥90 days	3.97 (0.87-28.9)
228	Hoffman 2017	Opioid duration	Opioid treatment ≥90 days	5.12 (1.63-19.62)
229	Inacio 2016	Gender	Female	1.40 (1.00 to 1.96)
230	Inacio 2016	Cause of pain	Back pain	3.90 (2.85 to 5.33)
231	Inacio 2016	Mental health	Depression	1.70 (1.20 to 2.41)
232	Inacio 2016	Substance misuse	Alcohol abuse	2.16 (0.75 to 6.22)
233	Inacio 2016	Mental health	Psychoses	1.39 (0.65 to 2.96)
234	Inacio 2016	Mental health	Anxiety	1.00 (0.66 to 1.50)
235	Inacio 2016	Comorbidity	Migraine	5.11 (1.08 to 24.18)
236	Inacio 2016	Comorbidity	Liver mild disease	4.33 (1.08 to 17.35)
237	Inacio 2016	Comorbidity	Weight loss	2.60 (1.06 to 6.39)
238	Inacio 2016	Comorbidity	Dementia	2.19 (1.04 to 4.61)
239	Inacio 2016	Comorbidity	Gastric acid disease	1.62 (1.16 to 2.25)
240	Inacio 2016	Comorbidity	Hyperlipidaemia	1.38 (1.00 to 1.91) 0.048
241	Inacio 2016	Comorbidity	Diabetes with complications	1.86 (0.97 to 3.57) 0.063
242	Inacio 2016	Comorbidity	Others	<1.6 NS
243	Inacio 2016	Benzo	hypnotics and sedatives (prior use)	1.56 (1.13 to 2.16)
244	Inacio 2016	Nonopioid pain tx	antineuropathic pain (prior use)	3.11 (2.05 to 4.72)
245	Inacio 2016	Nonopioid pain tx	muscle relaxants (prior use)	1.95 (0.39 to 9.74)
246	Inacio 2016	Nonpain tx	corticosteroids	1.17 (0.79 to 1.74)
247	Jain 2018	Opioid use	Preoperative chronic opioid therapy	8.08 7.40–8.80 <0.001
248	Jain 2018	Mental health	Anxiety	1.23 1.14–1.34 <0.001

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
249	Jain 2018	Mental health	Depression	1.28 1.19–1.39 <0.001
250	Jain 2018	Cause of pain	Inflammatory arthritis	1.35 1.27–1.45 <0.001
251	Jain 2018	Tobacco	Tobacco use disorder	1.48 1.34–1.63 <0.001
252	Jain 2018	Substance misuse	Drug abuse/dependence	1.98 1.64–2.4
253	Jain 2018	Race/ethnicity	African-American	1.24 1.11–1.4 <0.001
254	Jain 2018	Gender	Female	1.09 1.03–1.16 0.005
255	Jain 2018	Insurance	Medicare advantage	1.73 1.57–1.9 <0.001
256	Jain 2018	Age	Age >80	0.45 0.42–0.49 <0.001
257	Jeffery 2018	Opioid stewardship	Nonconcordant	1.30 (1.18–1.42)
258	Jeffery 2018	Opioid stewardship	Nonconcordant	4.42 (4.18–4.66)
259	Jena 2014	# Prescribers or pharmacists	1 opioid prescriber	1.64 (1.59 to 1.69)
260	Jena 2014	# Prescribers or pharmacists	2 opioid prescribers	1.97 (1.92 to 2.02)
261	Jena 2014	# Prescribers or pharmacists	3 opioid prescribers	2.33 (2.25 to 2.41)
262	Jena 2014	# Prescribers or pharmacists	>=4 opioid prescribers	3.24 (3.14 to 3.33)
263	Jena 2014	Age	Age: 65-74	1.55 (1.53 to 1.57)
264	Jena 2014	Age	Age: 75-84	1.32 (1.31 to 1.34)
265	Jena 2014	Race/ethnicity	Race: Non-Hispanic black	1.20 (1.18 to 1.22)
266	Jena 2014	Gender	Female	0.98 (0.97 to 0.99)
267	Jena 2014	Residence	Rural	0.81 (0.68 to 0.97)
268	Jena 2014	Income	Median household income in zipcode	1.03 (1.03 to 1.04)
269	Jena 2014	Income	Low-income subsidy only	0.88 (0.87 to 0.90)
270	Jena 2014	Income	Medicare-Medicaid dual eligible	0.91 (0.90 to 0.91)
271	Jena 2014	Nonpain tx	Anti-neoplastic agents	1.17 (1.15 to 1.92)
272	Jena 2014	Nonpain tx	Stimulants	1.04 (1.01 to 1.07)
273	Jena 2014	Nonpain tx	Psychotherapeutic/neurological agents	0.87 (0.86 to 0.89)
274	Jena 2014	Nonpain tx	Central nervous system drugs	1.10 (1.09 to 1.10)
275	Jena 2014	Nonpain tx	Neuromuscular agents	1.28 (1.27 to 1.29)
276	Jena 2014	Nonopioid pain tx	Non-narcotic analgesic	1.26 (1.25 to 1.27)
277	Jena 2014	Insurance	Medicare Advantage	1.07 (1.06 to 1.08)
278	Jena 2014	Opioid stewardship	State prescription drug monitoring program	1.01 (0.99 to 1.02)
279	Karttunen 2019	Comorbidity	Alzheimer disease	0.63 (0.60-0.66)
280	Karttunen 2019	Age	Age ≥ 80	0.92 (0.87-0.97)
281	Karttunen 2019	Income	Socioeconomic position: Medium	1.06 (1.00-1.12)
282	Karttunen 2019	Income	Socioeconomic position: Low	1.27 (1.15-1.41)

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
283	Karttunen 2019	Comorbidity	Cardiovascular disease	1.27 (1.20-1.34)
284	Karttunen 2019	Comorbidity	Diabetes	1.17 (1.08-1.26)
285	Karttunen 2019	Comorbidity	Asthma/COPD	1.28 (1.18-1.38)
286	Karttunen 2019	Cause of pain	Rheumatoid arthritis	1.39 (1.25-1.54)
287	Karttunen 2019	Comorbidity	History of hip fracture	1.60 (1.38-1.85)
288	Karttunen 2019	Comorbidity	Osteoporosis	1.13 (1.02-1.26)
289	Karttunen 2019	Mental health	Depression or bipolar disorder	1.13 (1.02-1.26
290	Karttunen 2019	Mental health	Schizophrenia	0.78 (0.64-0.95)
291	Karttunen 2019	Substance misuse	History of substance abuse	1.32 (1.16-1.52)
292	Karttunen 2019	Cause of pain	Active cancer	1.78 (1.62-1.96)
293	Karttunen 2019	Benzo	History of long-term benzodiazepine use	2.24 (2.11-2.37)
294	Kuo 2016	Opioid type	Schedule II opioid use >=90 d	1.74 (1.62-1.86)
295	Kuo 2016	Opioid type	Schedule III opioid use >=90 d	1.46 (1.38-1.54)
296	Kuo 2016	Opioid type	Schedule II opioid use >=90 d	1.78 (1.66-1.90)
297	Kuo 2016	Opioid type	Schedule III opioid use >=90 d	1.47 (1.40-1.54)
298	Lalic 2018	Gender	Male	0.71 (0.63-0.81)
299	Lalic 2018	Income	Govt subsidy	1.54 (1.37-1.74)
300	Lalic 2018	Opioid type	Strong opioid	1.51 (1.32-1.73)
301	Lalic 2018	Opioid type	Transdermal opioid	4.24 (3.85-4.68)
302	Lalic 2018	Opioid amount	MEq 250-499	1.68 (1.54-1.85)
303	Lalic 2018	Opioid amount	MEq 500-749	1.77 (1.28-2.45)
304	Lalic 2018	Opioid amount	MEq ≥750	2.20 (1.84-2.63)
305	Lalic 2018	Comorbidity	1-2 comorbidities	1.69 (0.84-3.84)
306	Lalic 2018	Comorbidity	3-4 comorbidities	2.00 (1.01-3.94)
307	Lalic 2018	Comorbidity	>=5 comorbidities	1.69 (0.86-3.33)
308	Lalic 2018	Mental health	Depression	1.53 (1.43-1.64)
309	Lalic 2018	Mental health	Psychotic illness	2.60 (2.29-2.95)
310	Lalic 2018	Substance misuse	Alcohol dependence	0.66 (0.20-2.14)
311	Lalic 2018	Comorbidity	Migraine	0.59 (0.31-1.12)
312	Lalic 2018	Tobacco	Nicotine dependence	1.80 (1.44-2.24)
313	Lalic 2018	Benzo	Benzodiazapines (prior use)	1.27 (1.18-1.37)
314	Lalic 2018	Nonopioid pain tx	Paracetamol (prior use)	2.15 (2.01-2.31)
315	Lalic 2018	Nonopioid pain tx	NSAIDs (prior use)	1.17 (1.10-1.25)
316	Lalic 2018	Nonopioid pain tx	Pregabalin (prior use)	1.55 (1.40-1.72)
317	Lalic 2018	Nonpain tx	Stimulants (prior use)	0.94 (0.28-3.19)
318	Lindestrand 2015	Gender	Male	NS
319	Lindestrand 2015	Age	Age >=82	NS

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
320	Lindestrand 2015	Social	Home dwelling	NS
321	Lindestrand 2015	Healthcare utilization	Admitted to geriatric ward postoperatively	1.69 (0.96–2.94) 0.07
322	Lindestrand 2015	Cause of pain	Pertrochanteric fracture	NS
323	Lindestrand 2015	Comorbidity	ASA score >2,	NS
324	Lindestrand 2015	Cause of pain	Osteoporosis,	2.38 (1.16–4.76) <0.05
325	Lindestrand 2015	Cause of pain	Cancer diagnosis,	NS
326	Lindestrand 2015	Cause of pain	Active cancer	3.13 (0.85–11.11) 0.09
327	Lindestrand 2015	Opioid use	Opioid usage before admission	5.88 (3.23–11.11)
328	Lindestrand 2015	Opioid stewardship	Tapering plan	0.56 (0.32–0.96) <0.05
329	Lo-Ciganic 2019	Opioid amount	Total MME	1.0
330	Lo-Ciganic 2019	Substance misuse	Hx SUD/AUD	0.9
331	Lo-Ciganic 2019	Opioid amount	Average daily MME	0.82
332	Lo-Ciganic 2019	Age	Age (Medicare)	0.69
333	Lo-Ciganic 2019	Comorbidity	Disability status	0.61
334	Lo-Ciganic 2019	Opioid amount	No. opioid fills	0.6
335	Lo-Ciganic 2019	Miscellaneous	Others	<40%
336	Loeb 2020	Cause of pain	Cancer risk category (prostate), distant mets (eg)	9.66 (2.08-50.0) 0.003
337	Loeb 2020	Comorbidity	Charlson Comorbidity Index 3+	3.38 (1.30-7.27) 0.004
338	Loeb 2020	Social	Unmarried	1.39 (1.05-1.84) 0.02
339	Loeb 2020	Education	Education, high	0.74 (0.52-1.06) 0.10
340	McDermott 2019	Age	Age 70-74	0.76 (0.39-1.51)
341	McDermott 2019	Age	Age >=75	0.48 (0.23-0.98)
342	McDermott 2019	Gender	Female	0.47 (0.24-0.91)
343	McDermott 2019	Race/ethnicity	Non-(White, non-Hispanic)	1.26 (0.61-2.61)
344	McDermott 2019	Social	Non-married	2.22 (1.19-4.14)
345	McDermott 2019	Residence	Nonmetropolitan	0.91 (0.41-1.96)
346	McDermott 2019	Cause of pain	Tumor stages, treatments, types, etc.	NS
347	McDermott 2019	Comorbidity	Comorbidity index 1	1.85 (0.94-3.63)
348	McDermott 2019	Comorbidity	Comorbidity index >=2	1.14 (0.56-2.34)
349	McDermott 2019	Income	Median income level, lowest quartile	0.90 (0.37-2.22)
350	McDermott 2019	Opioid use	Prior opioid use	3.56 (1.95-6.50)
351	McDermott 2019	Tobacco	History of tobacco use	3.84 (1.44-10.24)
352	McDermott 2019	Substance misuse	History of alcohol/substance abuse	0.37 (0.12-1.12)
353	McDermott 2019	Opioid type	First opioid prescribed: Codeine	0.32 (0.08-1.21)
354	McDermott 2019	Opioid type	First opioid prescribed: Oxycodone	0.26 (0.10-0.67)
355	McDermott 2019	Opioid amount	Initial high-dose opioid use	2.82 (1.41-5.65)
356	McDermott 2019	Opioid type	Initial long-acting opioid use	1.83 (0.87-3.85)

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
357	Musich 2019	Gender	Female	1.19 <0.0001
358	Musich 2019	Age	Age 70-74	0.9 0.0003
359	Musich 2019	Age	Age 75-79	0.88 0.0002
360	Musich 2019	Age	Age 80-84	0.94 0.1
361	Musich 2019	Age	Age ≥85	1.19 <0.0001
362	Musich 2019	omitted	PCP per 100,000	1 0.07
363	Musich 2019	Race/ethnicity	Minority low	1.06 0.22
364	Musich 2019	Race/ethnicity	Minority medium	1.04 0.39
365	Musich 2019	Income	Income low	1.49 <0.0001
366	Musich 2019	Income	Income medium	1.27 <0.0001
367	Musich 2019	Residence	Urban	0.9 0.0001
368	Musich 2019	omitted	Midwest	1.13 <0.0001
369	Musich 2019	omitted	Northeast	0.84 <0.0001
370	Musich 2019	omitted	West	1.22 <0.0001
371	Musich 2019	Insurance	Plan type: medium coverage	1.26 <0.0001
372	Musich 2019	Insurance	Plan type: other (<medium)	1.05 0.11
373	Musich 2019	Comorbidity	Pre-period HCC Score 0.50 to <1.20 (Hierarchical Condition Category)	1.58 <0.0001
374	Musich 2019	Comorbidity	Pre-period HCC Score 1.20 to <2.80	2.49 <0.0001
375	Musich 2019	Comorbidity	Pre-period HCC Score ≥2.8	4.34 <0.0001
376	Musich 2019	Opioid type	Index opioid category = 1: Long-acting	26.24 <0.0001
377	Musich 2019	Opioid type	Index opioid category = 6: Tramadol	3.6 <0.0001
378	Musich 2019	Cause of pain	1st opioid >30 days after chronic back pain	2.17 <0.0001
379	Musich 2019	Cause of pain	1st opioid within 30 days after new back pain	1.78 <0.0001
380	Musich 2019	Cause of pain	1st opioid within 30 days after TKA	1.02 0.8
381	Musich 2019	Cause of pain	1st opioid within 30 days after trauma	0.63 <0.0001
382	Musich 2019	Nonopioid pain tx	Muscle relaxant use	2.83 <0.0001
383	Musich 2019	Nonpain tx	Antipsychotic use	1.43 <0.0001
384	Musich 2019	Nonopioid pain tx	NSAID use	1.62 <0.0001
385	Musich 2019	Nonpain tx	Sleep medication use	1.79 <0.0001
386	Musich 2019	Nonopioid pain tx	Physical therapy use	1.43 <0.0001
387	Musich 2019	Benzo	Benzodiazepine in post only (new)	2.21 <0.0001
388	Musich 2019	Benzo	Benzodiazepine use in pre and post	1.26 <0.0001
389	Musich 2019	Benzo	Benzodiazepine use in pre only	0.75 <0.0001
390	Musich 2019	Mental health	Depression in post only (new)	1.77 <0.0001
391	Musich 2019	Mental health	Depression in pre and post	1.38 <0.0001
392	Musich 2019	Mental health	Depression in pre only	1.18 0.0006
393	Musich 2019	Mental health	Anxiety in post only (new)	1.36 <0.0001

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
394	Musich 2019	Mental health	Anxiety in pre and post	1.26 <0.0001
395	Musich 2019	Mental health	Anxiety in pre only	1.15 0.001
396	Namba 2018	Opioid amount	Preoperative number of opioid prescriptions	1.09 (1.09-1.09) <0.001
397	Namba 2018	Nonopioid pain tx	Preoperative NSAID use	1.04 (1.01-1.08) 0.011
398	Namba 2018	Gender	Female	1.03 (1.00-1.07) 0.092
399	Namba 2018	Age	Age (per 10-y increment) (3/4 >=61)	0.91 (0.89-0.93) <0.001
400	Namba 2018	Race/ethnicity	Asian	0.65 (0.59-0.72) <0.001
401	Namba 2018	Race/ethnicity	Black	1.08 (1.02-1.14) 0.009
402	Namba 2018	Race/ethnicity	Hispanic	1.02 (0.98-1.07) 0.343
403	Namba 2018	Comorbidity	BMI (per 5 point increment)	1.02 (1.01-1.03) 0.007
404	Namba 2018	Mental health	Anxiety	1.09 (1.05-1.14) <0.001
405	Namba 2018	Mental health	Bipolar	0.88 (0.77-1.00) 0.05
406	Namba 2018	Mental health	Depression	1.17 (1.12-1.23) <0.001
407	Namba 2018	Opioid duration	Opioid dependency	0.55 (0.49-0.62) <0.001
408	Namba 2018	Mental health	PTSD	1.44 (1.22-1.69) <0.001
409	Namba 2018	Substance misuse	Substance abuse	1.28 (1.21-1.35) <0.001
410	Namba 2018	Comorbidity	Diabetes	1.07 (1.04-1.11) <0.001
411	Namba 2018	Comorbidity	AIDS	0.37 (0.26-0.53) <0.001
412	Namba 2018	Comorbidity	Deficiency anemia	1.06 (1.00-1.12) 0.044
413	Namba 2018	Comorbidity	Rheumatoid arthritis	1.25 (1.15-1.36) <0.001
414	Namba 2018	Comorbidity	Chronic blood loss anemia	0.89 (0.78-1.01) 0.083
415	Namba 2018	Comorbidity	Congestive heart failure	1.2 (1.09-1.33) <0.001
416	Namba 2018	Comorbidity	Chronic lung disease	1.06 (1.00-1.11) 0.033
417	Namba 2018	Comorbidity	Coagulopthy	1.19 (1.05-1.35) 0.008
418	Namba 2018	Comorbidity	Hypertension	1.09 (1.04-1.14) 0.001
419	Namba 2018	Comorbidity	Hypothyroidism	0.99 (0.94-1.05) 0.858
420	Namba 2018	Comorbidity	Liver disease	1.17 (1.04-1.3) 0.007
421	Namba 2018	Comorbidity	Fluid and electrolyte disorders	1.04 (0.96-1.12) 0.31
422	Namba 2018	Comorbidity	Other neurological disorders	1.19 (1.10-1.29) <0.001
423	Namba 2018	Comorbidity	Paralysis	0.86 (0.69-1.06) 0.152
424	Namba 2018	Comorbidity	Peripheral vascular disease	1.12 (1.03-1.22) 0.008
425	Namba 2018	Comorbidity	Pulmonary circulation disorder	0.96 (0.78-1.17) 0.667
426	Namba 2018	Comorbidity	Renal failure	1.05 (0.98-1.12) 0.166
427	Namba 2018	Comorbidity	Peptic ulcer disease bleeding	1.17 (0.69-2.00) 0.552
428	Namba 2018	Comorbidity	Valvular disease	1.06 (0.95-1.18) 0.313
429	Namba 2018	Comorbidity	Weight loss	1.01 (0.80-1.28) 0.91
430	Namba 2018	Cause of pain	Arthritis	1.07 (0.96-1.18) 0.21

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
431	Namba 2018	Cause of pain	Back pain	1.35 (1.29-1.41) <0.001
432	Namba 2018	Cause of pain	Carpal tunel	0.75 (0.65-0.87) <0.001
433	Namba 2018	Cause of pain	Costochondritis and intracostal muscle injury	0.93 (0.60-1.44) 0.754
434	Namba 2018	Comorbidity	Dementia	0.72 (0.62-0.85) <0.001
435	Namba 2018	Cause of pain	Fibromyalgia	1.15 (1.06-1.25) 0.001
436	Namba 2018	Cause of pain	Fractures and contusions	0.96 (0.85-1.08) 0.475
437	Namba 2018	Cause of pain	Joint pain	0.94 (0.90-0.98) 0.003
438	Namba 2018	Cause of pain	Limb-extremity pain	1.01 (0.89-1.15) 0.84
439	Namba 2018	Cause of pain	Neck pain	1.11 (1.03-1.19) 0.007
440	Namba 2018	Cause of pain	Osteoarthritis	1.06 (0.97-1.16) 0.17
441	Namba 2018	Cause of pain	Other musculoskeletal pain	1.14 (0.95-1.36) 0.157
442	Namba 2018	Cause of pain	Nonspecific chronic pain	1.08 (1.04-1.13) <0.001
443	Nelson 2020	Age	Age 66-70	1.55 (1.16-2.06) 0.004 (overall age)
444	Nelson 2020	Age	Age 71-75	1.09 (0.81-1.46) 0.004 (overall age)
445	Nelson 2020	Age	Age 76-80	1.25 (0.93-1.69) 0.004 (overall age)
446	Nelson 2020	Gender	Female	1.02 (0.84-1.23) 0.837
447	Nelson 2020	Race/ethnicity	Hispanic	1.33 (0.90-1.97) 0.235 (overall race)
448	Nelson 2020	Race/ethnicity	Non-Hispanic Black	1.00 (0.67-1.51) 0.235 (overall race)
449	Nelson 2020	Race/ethnicity	Non-Hispanic Other	0.79 (0.54-1.15) 0.235 (overall race)
450	Nelson 2020	Residence	Metropolitan	1.02 (0.81-1.29) 0.15 (overall residence)
451	Nelson 2020	Residence	Urban	1.45 (0.97-2.18) 0.15 (overall residence)
452	Nelson 2020	Residence	Less urban	0.80 (0.56-1.15) 0.15 (overall residence)
453	Nelson 2020	Residence	Rural/unknown	0.93 (0.53-1.62) 0.15 (overall residence)
454	Nelson 2020	Social	Not married	0.99 (0.82-1.21) 0.457
455	Nelson 2020	omitted	HS educ in zip code, no 5.66-10.5%	1.09 (0.83-1.42) <0.001 (overall)
456	Nelson 2020	omitted	HS educ in zip code, no 10.5-19.35%	1.16)0.86-1.56) <0.001 (overall)

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
457	Nelson 2020	omitted	HS educ in zip code, no >=19.35%	1.86 (1.32-2.61) <0.001 (overall)
458	Nelson 2020	Income	Below poverty line in zip code 5.24-10.03%	1.15 (0.88-1.50) 0.647 (overall)
459	Nelson 2020	Income	Below poverty line in zip code 10.03-18.19%	1.11 (0.82-1.51) 0.647 (overall)
460	Nelson 2020	Income	Below poverty line in zip code >=18.19%	1.00 (0.70-1.43) 0.647 (overall)
461	Nelson 2020	Cause of pain	Lung cancer stage, various	0.667 (overall)
462	Nelson 2020	Cause of pain	Lung surgery type, various	0.341 (overall)
463	Nelson 2020	Cause of pain	Thoroscopic surgery	0.75 (0.62-0.90) 0.003
464	Nelson 2020	Nonpain tx	Adjuvant radiation	1.36 (1.06-1.74) 0.037 (overall)
465	Nelson 2020	Nonpain tx	Neoadjuvant radiation	1.47 (0.70-3.09) 0.037 (overall)
466	Nelson 2020	Nonpain tx	Adjuvant chemotherapy	1.87 (1.49-2.33) <0.001 (overall)
467	Nelson 2020	Nonpain tx	Neoadjuvant chemotherapy	0.87 (0.48-1.56) <0.001 (overall)
468	Nelson 2020	Cause of pain	Lung cancer grade, various	0.213 (overall)
469	Nelson 2020	Comorbidity	Charlson comorbidity 1	1.34 (1.10-1.64) 0.010 (overall)
470	Nelson 2020	Comorbidity	Charlson comorbidity 2+	1.27 (1.00-1.60) 0.010 (overall)
471	Park 2010	Age	Age (>=65)	-0.157 0.201
472	Park 2010	Gender	Male	3.102 0.086
473	Park 2010	Race/ethnicity	Minority	0.102 0.929
474	Park 2010	Cause of pain	Cancer	0.512 0.774
475	Park 2010	Pain	Pain severity (Brief Pain Inventory (BPI))	0.226 0.043
476	Park 2010	Pain	Duration of pain (6 mo or longer)	2.956 0.391
477	Park 2010	Activities of Daily Living	Older American Resources and Services Activities of Daily Living (OARS ADL)	-0.498 0.007
478	Park 2010	Substance misuse	CAGE	1.187 0.024
479	Park 2010	Mental health	Center for Epidemiologic Studies Depression Scale-10 (CESD-10)	0.366 0.024
480	Park 2010	Mental health	Existential Well-Being Subscale of the Spiritual Well-Being Scale (EWB)	-0.024 0.697
481	Park 2010	Social	Lubben Social Network Scale (LSNS)	-0.073 0.585

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
482	Park 2010	Social	ENRICH Social Support Instrument (ESSI)	-0.268 0.072
483	Rao 2018	Gender	Female	1.10 (1.03-1.17) 0.006
484	Rao 2018	Race/ethnicity	African American	0.88 (0.78-1.00) 0.043
485	Rao 2018	Race/ethnicity	Asian	1.17 (0.95-1.43) 0.133
486	Rao 2018	Race/ethnicity	Hispanic	1.02 (0.92-1.12) 0.757
487	Rao 2018	Race/ethnicity	Other race	1.60 (1.29-1.98) <0.001
488	Rao 2018	Comorbidity	BMI 30-34.9	1.01 (0.93-1.09) 0.830
489	Rao 2018	Comorbidity	BMI ≥35	0.96 (0.88-1.06) 0.409
490	Rao 2018	Comorbidity	ASA class ≥3	1.15 (1.06-1.23) <0.001
491	Rao 2018	Opioid amount	Preoperative opioid Rx: 1-4 Rx	2.15 (1.85-2.51) <0.001
492	Rao 2018	Opioid amount	Preoperative opioid Rx: >=5 Rx	9.83 (8.53-11.32) <0.001
493	Rao 2018	Comorbidity	Chronic blood loss anemia	0.78 (0.60-1.02) 0.068
494	Rao 2018	Comorbidity	Chronic pulmonary disease	1.04 (0.96-1.13) 0.296
495	Rao 2018	Comorbidity	Coagulopathy	1.24 (1.00-1.53) 0.054
496	Rao 2018	Comorbidity	Congestive heart failure	1.08 (0.93-1.25) 0.335
497	Rao 2018	Comorbidity	Deficiency anemia	1.07 (0.97-1.19) 0.154
498	Rao 2018	Comorbidity	Diabetes	0.96 (0.87-1.06) 0.443
499	Rao 2018	Comorbidity	Fluid and electrolyte disorders	1.03 (0.92-1.17) 0.571
500	Rao 2018	Comorbidity	Hypertension	1.05 (0.97-1.15) 0.230
501	Rao 2018	Comorbidity	Hypothyroidism	1.00 (0.90-1.10) 0.977
502	Rao 2018	Comorbidity	Liver disease	1.01 (0.86-1.20) 0.867
503	Rao 2018	Comorbidity	Neurodegenerative disorders	1.17 (1.04-1.31) 0.010
504	Rao 2018	Comorbidity	Paralysis	0.71 (0.47-1.08) 0.107
505	Rao 2018	Comorbidity	Peripheral vascular disease	0.92 (0.82-1.02) 0.096
506	Rao 2018	Comorbidity	Renal failure	0.97 (0.88-1.06) 0.482
507	Rao 2018	Comorbidity	Rheumatoid arthritis/collagen vascular disease	1.03 (0.90-1.17) 0.680
508	Rao 2018	Comorbidity	Valvular disease	1.00 (0.86-1.16) 0.965
509	Rao 2018	Comorbidity	Weight loss	0.92 (0.75-1.14) 0.461
510	Rao 2018	Mental health	Anxiety	1.11 (1.03-1.20) 0.005
511	Rao 2018	Mental health	Bipolar disorder	0.88 (0.72-1.06) 0.182
512	Rao 2018	Mental health	Dementia and psychosis	1.03 (0.94-1.13) 0.498
513	Rao 2018	Mental health	Depression	1.08 (1.00-1.17) 0.042
514	Rao 2018	Opioid duration	Opioid dependence	1.23 (1.05-1.43) 0.010
515	Rao 2018	Mental health	Post-traumatic stress disorder	1.25 (0.96-1.63) 0.099
516	Rao 2018	Substance misuse	Substance abuse	1.17 (1.07-1.28) <0.001
517	Rao 2018	Cause of pain	Arthritis	0.92 (0.83-1.01) 0.084
518	Rao 2018	Cause of pain	Chronic back pain, h/o	1.21 (1.12-1.29) <0.001

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
519	Rao 2018	Cause of pain	Carpal tunnel	1.06 (0.85-1.32) 0.630
520	Rao 2018	Cause of pain	Fibromyalgia	1.20 (1.04-1.38) 0.013
521	Rao 2018	Cause of pain	Fractures and contusions with chronic pain, h/o	0.86 (0.75-0.99) 0.040
522	Rao 2018	Cause of pain	Limb extremity pain, chronic, h/o	0.70 (0.58-0.85) <0.001
523	Rao 2018	Cause of pain	Neck pain, chronic, h/o	0.99 (0.89-1.11) 0.856
524	Rao 2018	Cause of pain	Osteoarthritis	0.98 (0.88-1.08) 0.651
525	Rao 2018	Cause of pain	Other musculoskeletal pain, chronic, h/o	1.07 (0.86-1.34) 0.523
526	Rao 2018	Cause of pain	Abdominal pain/hernia, chronic, h/o	0.92 (0.79-1.08) 0.328
527	Rao 2018	Cause of pain	General chronic pain	1.38 (1.28-1.50) <0.001
528	Rao 2018	Cause of pain	Kidney/gall stones pain, h/o	1.18 (0.91-1.53) 0.202
529	Rao 2018	Cause of pain	Migraines	1.08 (0.92-1.26) 0.329
530	Rao 2018	Cause of pain	Neurologic pain, chronic	0.91 (0.83-1.01) 0.068
531	Rao 2018	Cause of pain	Tension headache, chronic, h/o	1.15 (0.92-1.45) 0.219
532	Santosa 2020	Opioid amount	High-risk prescribing: Opioid overlap	5.15 (4.03 6.59) <0.001
533	Santosa 2020	Benzo	High-risk prescribing: Benzodiazepine overlap	4.83 (4.08 5.71) <0.001
534	Santosa 2020	Opioid type	High-risk prescribing: Use of long-acting opioids	2.87 (2.18 3.76) <0.001
535	Santosa 2020	Opioid amount	High-risk prescribing: Opioid doses ≥100 MME	1.22 (1.09 1.36) <0.001
536	Santosa 2020	Cause of pain	Major surgery	1.24 (1.17 1.31) <0.001
537	Santosa 2020	Opioid prescription	Filled a prescription for opioids within 30 days before surgery	1.67 (1.58 1.77) <0.001
538	Santosa 2020	Opioid amount	Total prescription filled between the month before surgery and 2 weeks after discharge >=75th percentile (300 OMEs)	1.44 (1.37 1.52) <0.001
539	Santosa 2020	Benzo	Filled benzos, sedatives, hypnotics, anxiolytic prescriptions within 30 days before surgery	1.24 (1.14 1.35) <0.001
540	Santosa 2020	Comorbidity	Filled Anticoagulant Prescriptions within 30 days before surgery	1.03 (0.77 1.39) 0.822
541	Santosa 2020	Age	Age 70-74	0.94 (0.88 1.00) 0.068
542	Santosa 2020	Age	Age 75-79	1.02 (0.95 1.10) 0.513
543	Santosa 2020	Age	Age 80-84	1.04 (0.96 1.13) 0.330
544	Santosa 2020	Age	Age ≥85	1.09 (0.99 1.21) 0.085
545	Santosa 2020	Gender	Female	1.02 (0.97 1.07) 0.413
546	Santosa 2020	Race/ethnicity	Black	1.23 (1.12 1.36) <0.001
547	Santosa 2020	Race/ethnicity	Hispanic	1.07 (0.91 1.25) 0.401
548	Santosa 2020	Race/ethnicity	Race, Other	0.64 (0.54 0.75) <0.001
549	Santosa 2020	Residence	Metropolitan counties	1.02 (0.96 1.08) 0.549
550	Santosa 2020	omitted	East south central	1.27 (1.15 1.40) <0.001
551	Santosa 2020	omitted	Middle Atlantic	0.85 (0.77 0.93) 0.001
552	Santosa 2020	omitted	Mountain	1.11 (1.00 1.24) 0.061
553	Santosa 2020	omitted	New England	0.85 (0.74 0.97) 0.016
554	Santosa 2020	omitted	Pacific	0.95 (0.87 1.04) 0.292

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
555	Santosa 2020	omitted	South Atlantic	1.01 (0.93 1.10) 0.821
556	Santosa 2020	omitted	West north central	1.01 (0.92 1.12) 0.812
557	Santosa 2020	omitted	West south central	1.17 (1.07 1.28) 0.001
558	Santosa 2020	Income	Medicaid eligible	1.45 (1.35 1.55) <0.001
559	Santosa 2020	Comorbidity	Charlson comorbidity index 1, 2	1.18 (1.11 1.27) <0.001
560	Santosa 2020	Comorbidity	Charlson comorbidity index CCI 3, 4	1.41 (1.31 1.52) <0.001
561	Santosa 2020	Comorbidity	Charlson comorbidity index ≥5	1.71 (1.58 1.84) <0.001
562	Santosa 2020	Tobacco	History of tobacco use	1.03 (0.97 1.09) 0.381
563	Santosa 2020	Mental health	Adjustment disorder	0.99 (0.82 1.18) 0.877
564	Santosa 2020	Mental health	Anxiety disorder	1.07 (1.00 1.15) 0.058
565	Santosa 2020	Mental health	Mood disorder	1.16 (1.09 1.24) <0.001
566	Santosa 2020	Mental health	Suicide or self-harm history	1.60 (1.05 2.44) 0.029
567	Santosa 2020	Mental health	Disruptive disorder	0.80 (0.56 1.13) 0.207
568	Santosa 2020	Mental health	Personality disorder	1.32 (0.90 1.93) 0.157
569	Santosa 2020	Mental health	Psychosis	0.97 (0.83 1.13) 0.689
570	Santosa 2020	Substance misuse	Alcohol or substance abuse disorders	1.38 (1.20 1.59) <0.001
571	Santosa 2020	Cause of pain	Arthritis pain	1.01 (0.95 1.07) 0.810
572	Santosa 2020	Cause of pain	Back pain	1.16 (1.07 1.27) 0.001
573	Santosa 2020	Cause of pain	Neck pain	0.92 (0.80 1.04) 0.181
574	Schepis 2019	Opioid use	Past-year Opioid use, without misuse	1.00 (0.73-1.37)
575	Schepis 2019	Opioid misuse	Past-year Opioid misuse	1.84 (1.07-3.19)
576	Shah 2019	Comorbidity	Years since cancer diagnosis	1.09 (1.08-1.10)
577	Shah 2019	Age	Age 75-84	0.96 (0.91-1.01)
578	Shah 2019	Age	Age >=85	0.83 (0.78-0.89)
579	Shah 2019	Gender	Female	1.40 (1.31-1.50)
580	Shah 2019	Race/ethnicity	Black	1.01 (0.93-1.10)
581	Shah 2019	Race/ethnicity	Hispanic	0.78 (0.73-0.83)
582	Shah 2019	Race/ethnicity	Other race	0.61 (0.52-0.73)
583	Shah 2019	Residence	Urban	1.10 (1.04-1.16)
584	Shah 2019	Residence	Rural	1.05 (0.90-1.23)
585	Shah 2019	Cause of pain	Breast cancer	1.06 (0.96-1.16)
586	Shah 2019	Cause of pain	Lung cancer	1.21 (1.06-1.37)
587	Shah 2019	Cause of pain	Colorectal cancer	0.99 (0.90-1.09)
588	Shah 2019	Opioid use	Opioid naïve	0.11 (0.10-0.11)
589	Shah 2019	Income	Medicaid eligible	1.57 (1.49-1.66)
590	Shah 2019	Comorbidity	Charlson Comorbidity Score ≥1	1.29 (1.23-1.36)
591	Shah 2019	Mental health	Depression	1.32 (1.23-1.41)

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
592	Shah 2019	Substance misuse	Alcohol abuse	1.27 (0.95-1.69)
593	Shah 2019	Substance misuse	Drug abuse	2.51 (1.96-3.22)
594	Shah 2019	Comorbidity	Years since cancer diagnosis	1.33 (1.32-1.35)
595	Shah 2019	Age	Age 75-84	1.03 (0.94-1.13)
596	Shah 2019	Age	Age >=85	0.97 (0.86-1.10)
597	Shah 2019	Gender	Female	1.50 (1.32-1.72)
598	Shah 2019	Race/ethnicity	Black	1.00 (0.86-1.18)
599	Shah 2019	Race/ethnicity	Hispanic	0.86 (0.76-0.97)
600	Shah 2019	Race/ethnicity	Other race	0.68 (0.50-0.91)
601	Shah 2019	Residence	Urban	1.21 (1.10-1.33)
602	Shah 2019	Residence	Rural	1.20 (0.92-1.57)
603	Shah 2019	Cause of pain	Breast cancer	1.00 (0.84-1.19)
604	Shah 2019	Cause of pain	Lung cancer	1.09 (0.83-1.43)
605	Shah 2019	Cause of pain	Colorectal cancer	0.99 (0.83-1.18)
606	Shah 2019	Income	Medicaid eligible	1.62 (1.46-1.81)
607	Shah 2019	Comorbidity	Charlson Comorbidity Score ≥1	1.53 (1.40-1.67)
608	Shah 2019	Mental health	Depression	1.35 (1.16-1.58)
609	Shah 2019	Substance misuse	Alcohol abuse	1.25 (0.63-2.50)
610	Shah 2019	Substance misuse	Drug abuse	1.76 (0.81-3.82)
611	Suda 2017	Gender	Female	1.08 0.384
612	Suda 2017	Age	Age 71-75	0.85 0.095
613	Suda 2017	Age	Age 76-80	0.63 <0.0001
614	Suda 2017	Age	Age 81-85	0.59 <0.0001
615	Suda 2017	Age	Age 86-90	0.47 <0.0001
616	Suda 2017	Age	Age >91	0.42 0.001
617	Suda 2017	Race/ethnicity	African American	0.76 0.053
618	Suda 2017	Race/ethnicity	Non-Hispanic	1.19 0.431
619	Suda 2017	Insurance	No copay	2.95 <0.0001
620	Suda 2017	Insurance	Some copay	1.94 <0.0001
621	Suda 2017	Residence	5-20 miles	1.12 0.235
622	Suda 2017	Residence	21-40 miles	1.29 0.007
623	Suda 2017	Residence	41-60 miles	1.37 0.004
624	Suda 2017	Residence	>60 miles	0.96 0.777
625	Suda 2017	Income	Median household income, per $10,000	0.87 0.001
626	Suda 2017	Income	Percent below poverty level, per %	0.99 0.038
627	Suda 2017	Residence	Rural	1.30 0.001
628	Suda 2017	Comorbidity	Hierarchical Condition Category (HCC) risk score, per point	1.10 <0.0001

Row	Author Year	Factor Category	Risk Factor	Estimate (95% CI) P
629	Suda 2017	Tobacco	Smoking	1.13 0.104
630	Suda 2017	Mental health	Suicide or self injury	0.87 0.830
631	Suda 2017	Mental health	Sleep disorder	2.00 <0.0001
632	Suda 2017	Mental health	Psychiatric diagnosis	2.30 <0.0001
633	Suda 2017	Substance misuse	Substance abuse	1.88 <0.0001
634	Suda 2017	Substance misuse	Alcohol abuse	1.02 0.854
635	Suda 2017	Healthcare utilization	Primary care (Medicare), per day (implied)	1.04 <0.0001
636	Suda 2017	Healthcare utilization	Specialty care (Medicare), per day (implied)	1.01 <0.0001
637	Suda 2017	Healthcare utilization	Length of stay (Medicare), per day (implied)	1.01 0.009
638	Taipale 2019	Opioid use	Opioid user	1.96 (1.27-3.02)
639	Taipale 2019	Opioid duration	1-60 d opioid use	2.37 (1.04-5.41)
640	Taipale 2019	Opioid duration	61-180 d opioid use	1.79 (0.82-3.89)
641	Taipale 2019	Opioid duration	181-365 d opioid use	1.43 (0.61-3.37)
642	Taipale 2019	Opioid duration	>365 d opioid use	2.59 (0.92-7.28)
643	Taipale 2019	Opioid type	Weak opioid	1.75 (0.91-3.35)
644	Taipale 2019	Opioid type	Buprenorphine	2.10 (1.41-3.13)
645	Taipale 2019	Opioid type	Strong opioid	2.89 (1.32-6.32)
646	Vozoris 2016	Opioid use	New opioid use	2.16 (1.61–2.88)
647	Vozoris 2016	Opioid use	New opioid use	1.76 (1.57–1.98)
648	Vozoris 2016	Opioid use	New opioid use	0.88 (0.83–0.94)
649	Vozoris 2016	Opioid use	New opioid use	1.14 (1.00–1.29)
650	Vozoris 2016	Opioid use	New opioid use	1.08 (0.97–1.21)
651	Vozoris 2016	Opioid use	New opioid use	0.99 (0.74–1.33)
652	Zeng 2019	Opioid type	Tramadol	2.00 (1.33, 3.01)
653	Zoorob 2018	Benzo	Benzodiazepine, %	1.356 <0.05
654	Zoorob 2018	Opioid use	Opioid %	1.124 <0.01
655	Zoorob 2018	Benzo	Benzod, %, * opioid, % (interaction)	1.077 <0.01
656	Zoorob 2018	Income	Income	1.001 >0.10
657	Zoorob 2018	Income	Poverty, %	1.128 <0.01
658	Zoorob 2018	Race/ethnicity	Hispanic, %	0.960 <0.01
659	Zoorob 2018	Race/ethnicity	Black, %	0.908 <0.01
660	Zoorob 2018	Residence	Rural	0.763 <0.01
661	Zoorob 2018	Education	Less than high school, %	1.119 <0.01

Table D-3c. Studies with multivariable analyses of associations: Other information

Row	Author Year	Metric	Comparator	Note
1	Al Dabbagh 2016	HR	<70	Outcome is a "good" outcome
2	Al Dabbagh 2016	HR	Male	ditto
3	Al Dabbagh 2016	HR	Closed	ditto
4	Alam 2012	OR	no prescription	
5	Brescia 2019	OR	No	
6	Brescia 2019	OR	Other CT surgery	
7	Brescia 2019	OR	Post-surgery Rx	
8	Brescia 2019	OR	(continuous)	
9	Brescia 2019	OR	(continuous)	
10	Brescia 2019	OR	(continuous)	
11	Brescia 2019	OR	Male	
12	Brescia 2019	OR	White	
13	Brescia 2019	OR	No	
14	Brescia 2019	OR	Old age	
15	Brescia 2019	OR	0-2	Similar, stronger for higher scores
16	Brescia 2019	OR	No	
17	Brescia 2019	OR	No	
18	Brescia 2019	OR	No	
19	Brescia 2019	OR	No	
20	Brescia 2019	OR	No	
21	Brescia 2019	OR	No	
22	Cancienne 2018	OR	Unclear	
23	Cancienne 2018	OR	Unclear	
24	Cancienne 2018	OR	Unclear	
25	Cancienne 2018	OR	Unclear	
26	Cancienne 2018	OR	Unclear	
27	Cancienne 2018	OR	No	
28	Cancienne 2018	OR	No	
29	Cancienne 2018	OR	No	
30	Cancienne 2018	OR	No	
31	Cancienne 2018	OR	No	
32	Cancienne 2018	OR	No	
33	Cancienne 2018	OR	No	
34	Cancienne 2018	OR	No	
35	Cancienne 2018	OR	No	
36	Cancienne 2018	OR	Female	
37	Cancienne 2018	OR	No	

Row	Author Year	Metric	Comparator	Note
38	Cancienne 2018	OR	No	
39	Cancienne 2018	OR	No	
40	Cancienne 2018	OR	No	
41	Cancienne 2018	OR	No	
42	Cancienne 2018	OR	No	
43	Carey 2018	RR	No possible misuse	
44	Carey 2018	RR	No possible misuse	
45	Carey 2018	RR	No possible misuse	
46	Carey 2018	RR	No possible misuse	
47	Carey 2018	RR	No possible misuse	
48	Carey 2018	RR	No possible misuse	
49	Carter 2019	OR	No	
50	Carter 2019	OR	>=85	
51	Carter 2019	OR	>=85	
52	Carter 2019	OR	Male	
53	Carter 2019	OR	(continuous)	
54	Carter 2019	OR	No	
55	Carter 2019	OR	No	
56	Carter 2019	OR	Medicare	
57	Carter 2019	OR	Medicare	
58	Carter 2019	OR	Middle quartiles	
59	Carter 2019	OR	Middle quartiles	
60	Carter 2019	OR	No	
61	Choi 2017	OR	No	
62	Choi 2017	OR	(continuous)	
63	Choi 2017	OR	Female	
64	Choi 2017	OR	Non-Hispanic White	
65	Choi 2017	OR	Non-Hispanic White	
66	Choi 2017	OR	Non-Hispanic White	
67	Choi 2017	OR	No	
68	Choi 2017	OR	No	
69	Choi 2017	OR	No	
70	Choi 2017	OR	(continuous)	
71	Choi 2017	OR	No	
72	Choi 2017	OR	None	
73	Choi 2017	OR	None	
74	Choi 2017	OR	No	

Row	Author Year	Metric	Comparator	Note
75	Choi 2017	OR	No	
76	Choi 2017	OR	No	
77	Choi 2017	OR	No	
78	Choi 2017	OR	No	
79	Choi 2019	OR	No use	
80	Choi 2019	OR	No use	
81	Choi 2019	OR	No use	
82	Choi 2019	OR	No use	
83	Choi 2019	Incident rate ratio	No use	
84	Choi 2019	Incident rate ratio	No use	
85	Choi 2019	Incident rate ratio	No use	
86	Choi 2019	Incident rate ratio	No use	
87	Cochran 2017	Incidence rate ratio	(continuous)	0-10 behaviors based on the Drug Abuse Screening Test-10 (DAST-10)
88	Cochran 2017	Incidence rate ratio	(continuous)	0 to 12 scores based on Alcohol Use Disorders Identification Test-C (AUDIT-C)
89	Cochran 2017	Incidence rate ratio	(continuous)	0 to 6 based on Patient Health Question-2 (PHQ-2)
90	Cochran 2017	Incidence rate ratio	(continuous)	0 to 4 based on the Primary Care-Posttraumatic Stress Disorder assessment
91	Cochran 2017	Incidence rate ratio	(continuous)	Subscale from Short-Form Survey 12 (SF-12)
92	Cochran 2017	Incidence rate ratio	(continuous)	Subscale from Short-Form Survey 12 (SF-12)
93	Cochran 2017	Incidence rate ratio	Male	
94	Cochran 2017	Incidence rate ratio	High school education or more	
95	Cochran 2017	Incidence rate ratio	Urban pharmacy	
96	Curtis 2017	OR	.	
97	Curtis 2017	OR	Female	
98	Curtis 2017	OR	African American	
99	Curtis 2017	OR	African American	
100	Curtis 2017	OR	No	
101	Curtis 2017	OR	No	
102	Curtis 2017	OR	No	
103	Curtis 2017	OR	No	
104	Curtis 2017	OR	No	
105	Curtis 2017	OR	No	
106	Curtis 2017	OR	No	
107	Curtis 2017	OR	No	
108	Curtis 2017	OR	No	

Row	Author Year	Metric	Comparator	Note
109	Curtis 2017	OR	No	
110	Curtis 2017	OR	No	
111	Curtis 2017	OR	No	
112	Curtis 2017	OR	No	
113	Curtis 2017	OR	No	
114	Curtis 2017	OR	No	
115	Curtis 2017	OR	No	
116	Curtis 2017	OR	No fill of NSAID	
117	Curtis 2017	OR	No fill of NSAID	
118	Curtis 2017	OR	No	
119	Curtis 2017	OR	No	
120	Curtis 2017	OR	Quartile 4 (highest)	
121	Curtis 2017	OR	Quartile 4 (highest)	
122	Curtis 2017	OR	Quartile 4 (highest)	
123	Daoust 2018	OR	Male	
124	Daoust 2018	OR	Fall	
125	Daoust 2018	OR	Fall	
126	Daoust 2018	OR	1 injury	
127	Daoust 2018	OR	1 injury	
128	Daoust 2018	OR	No	
129	Daoust 2018	OR	No	
130	Daoust 2018	OR	No	
131	Daoust 2018	OR	No	
132	Daoust 2018	OR	No	
133	Daoust 2018	OR	No	
134	Daoust 2018	OR	No	
135	Daoust 2018	OR	No	
136	Daoust 2018	OR	No	
137	Daoust 2018	OR	No	
138	Daoust 2018	OR	0 prescriptions	
139	Daoust 2018	OR	0 prescriptions	
140	Daoust 2018	OR	No	
141	Dasinger 2019	OR	No opioids	
142	Dasinger 2019	OR	No opioids	
143	Dasinger 2019	OR	No opioids	
144	Dasinger 2019	OR	No	
145	Dasinger 2019	OR	No	

Row	Author Year	Metric	Comparator	Note
146	Gold 2016	RRR	No	Multiple prescribers, fake Rx, stole, from friend or relative (free or bought), from drug dealer or internet, "some other way"
147	Gold 2016	RRR	60-64	ditto
148	Gold 2016	RRR	60-64	ditto
149	Gold 2016	RRR	60-64	ditto
150	Gold 2016	RRR	60-64	ditto
151	Gold 2016	RRR	60-64	ditto
152	Gold 2016	RRR	Male	ditto
153	Gold 2016	RRR	No college	ditto
154	Gold 2016	RRR	No college	ditto
155	Gold 2016	RRR	(continuous)	ditto
156	Gold 2016	RRR	(continuous)	ditto
157	Gold 2016	RRR	No	ditto
158	Gold 2016	RRR	No	ditto
159	Grigoras 2018	Coefficient	(continuous)	
160	Grigoras 2018	Coefficient	(continuous)	
161	Grigoras 2018	Coefficient	(continuous)	
162	Grigoras 2018	Coefficient	(continuous)	
163	Grigoras 2018	Coefficient	(continuous)	
164	Grigoras 2018	Coefficient	(continuous)	
165	Grigoras 2018	Coefficient	(continuous)	
166	Grigoras 2018	Coefficient	(continuous)	
167	Grigoras 2018	Coefficient	(continuous)	Top 25%
168	Grigoras 2018	Coefficient	(continuous)	
169	Grigoras 2018	Coefficient	(continuous)	
170	Grigoras 2018	Coefficient	(continuous)	
171	Grigoras 2018	Coefficient	(continuous)	
172	Grigoras 2018	Coefficient	(continuous)	
173	Grigoras 2018	Coefficient	(continuous)	
174	Grigoras 2018	Coefficient	(continuous)	
175	Grigoras 2018	Coefficient	(continuous)	
176	Grigoras 2018	Coefficient	(continuous)	
177	Grigoras 2018	Coefficient	(continuous)	
178	Grigoras 2018	Coefficient	(continuous)	
179	Grigoras 2018	Coefficient	(continuous)	
180	Grigoras 2018	Coefficient	(continuous)	
181	Grigoras 2018	Coefficient	(continuous)	

Row	Author Year	Metric	Comparator	Note
182	Grigoras 2018	Coefficient	(continuous)	
183	Hadlandsmyth 2018	RR	Male	No Long-Term Opioids Before TKA (model for + long term use generally has smaller associations)
184	Hadlandsmyth 2018	RR (est)	60-70	ditto
185	Hadlandsmyth 2018	RR	Caucasian	ditto
186	Hadlandsmyth 2018	RR	Caucasian	ditto
187	Hadlandsmyth 2018	RR	Normal weight	ditto
188	Hadlandsmyth 2018	RR	Normal weight	ditto
189	Hadlandsmyth 2018	RR	No	ditto
190	Hadlandsmyth 2018	RR	0-1	ditto
191	Hadlandsmyth 2018	RR	0-1	ditto
192	Hadlandsmyth 2018	RR	0-1	ditto
193	Hadlandsmyth 2018	RR	No	ditto
194	Hadlandsmyth 2018	RR	No	ditto
195	Hadlandsmyth 2018	RR	No	ditto
196	Hadlandsmyth 2018	RR	None	ditto
197	Hadlandsmyth 2018	RR	None	ditto
198	Hadlandsmyth 2018	RR	None	ditto
199	Hadlandsmyth 2018	RR	None	ditto
200	Hadlandsmyth 2018	RR	None	ditto
201	Hadlandsmyth 2018	RR	None	ditto
202	Hadlandsmyth 2018	RR	None	ditto
203	Hadlandsmyth 2018	RR	None	ditto
204	Hadlandsmyth 2018	RR	None	ditto
205	Hadlandsmyth 2018	RR	None	ditto
206	Hadlandsmyth 2018	RR	(continuous)	ditto
207	Hadlandsmyth 2018	RR	Bilateral	ditto
208	Hamina 2017	OR	No	
209	Hamina 2017	OR	Male	
210	Hamina 2017	OR	<80	
211	Hamina 2017	OR	High	
212	Hamina 2017	OR	High	
213	Hamina 2017	OR	No	
214	Hamina 2017	OR	No	
215	Hamina 2017	OR	No	
216	Hamina 2017	OR	No	
217	Hamina 2017	OR	No	

Row	Author Year	Metric	Comparator	Note
218	Hamina 2017	OR	No	
219	Hamina 2017	OR	No	
220	Hamina 2017	OR	No	
221	Hoffman 2017	HR	<90 days	
222	Hoffman 2017	HR	<90 days	
223	Hoffman 2017	HR	<90 days	
224	Hoffman 2017	HR	<90 days	
225	Hoffman 2017	HR	<90 days	
226	Hoffman 2017	HR	<90 days	
227	Hoffman 2017	HR	<90 days	
228	Hoffman 2017	HR	<90 days	
229	Inacio 2016	OR	Male	
230	Inacio 2016	OR	No	
231	Inacio 2016	OR	No	
232	Inacio 2016	OR	No	
233	Inacio 2016	OR	No	
234	Inacio 2016	OR	No	
235	Inacio 2016	OR	No	
236	Inacio 2016	OR	No	
237	Inacio 2016	OR	No	
238	Inacio 2016	OR	No	
239	Inacio 2016	OR	No	
240	Inacio 2016	OR	No	
241	Inacio 2016	OR	No	
242	Inacio 2016	OR	No	
243	Inacio 2016	OR	No	
244	Inacio 2016	OR	No	
245	Inacio 2016	OR	No	
246	Inacio 2016	OR	No	
247	Jain 2018	OR	No	
248	Jain 2018	OR	No	
249	Jain 2018	OR	No	
250	Jain 2018	OR	No	
251	Jain 2018	OR	No	
252	Jain 2018	OR	No	
253	Jain 2018	OR	No	
254	Jain 2018	OR	No	

Row	Author Year	Metric	Comparator	Note
255	Jain 2018	OR	No	
256	Jain 2018	OR	<=80	
257	Jeffery 2018	RR	Guideline concordant (≤3 d & ≤50 MME/d & not long acting)	ED setting
258	Jeffery 2018	RR	Guideline concordant (≤3 d & ≤50 MME/d & not long acting)	Non-ED setting
259	Jena 2014	OR	0 providers (implied)	
260	Jena 2014	OR	0 providers (implied)	
261	Jena 2014	OR	0 providers (implied)	
262	Jena 2014	OR	0 providers (implied)	
263	Jena 2014	OR	≥85	
264	Jena 2014	OR	≥85	
265	Jena 2014	OR	Non-Hispanic white	Other races smaller associations
266	Jena 2014	OR	Male	
267	Jena 2014	OR	Metropolitan area	
268	Jena 2014	OR	(continuous)	
269	Jena 2014	OR	Non-eligible for subsidy	
270	Jena 2014	OR	Non-eligible for subsidy	
271	Jena 2014	OR	No	
272	Jena 2014	OR	No	
273	Jena 2014	OR	No	
274	Jena 2014	OR	No	
275	Jena 2014	OR	No	
276	Jena 2014	OR	No	
277	Jena 2014	OR	No	
278	Jena 2014	OR	No	
279	Karttunen 2019	OR	No	
280	Karttunen 2019	OR	<80	Separate analyses for AD and no AD
281	Karttunen 2019	OR	High	ditto
282	Karttunen 2019	OR	High	ditto
283	Karttunen 2019	OR	No	ditto
284	Karttunen 2019	OR	No	ditto
285	Karttunen 2019	OR	No	ditto
286	Karttunen 2019	OR	No	ditto
287	Karttunen 2019	OR	No	ditto
288	Karttunen 2019	OR	No	ditto

Row	Author Year	Metric	Comparator	Note
289	Karttunen 2019	OR	No	ditto
290	Karttunen 2019	OR	No	ditto
291	Karttunen 2019	OR	No	ditto
292	Karttunen 2019	OR	No	ditto
293	Karttunen 2019	OR	No	ditto
294	Kuo 2016	OR	No	
295	Kuo 2016	OR	No	
296	Kuo 2016	OR	No	
297	Kuo 2016	OR	No	
298	Lalic 2018	OR	Female	2 models (65-84 yo; 85-99 yo); Stronger association chosen here
299	Lalic 2018	OR	No	ditto
300	Lalic 2018	OR	Weak opioid	ditto
301	Lalic 2018	OR	Oral opioid	ditto
302	Lalic 2018	OR	MEq <250	ditto
303	Lalic 2018	OR	MEq <250	ditto
304	Lalic 2018	OR	MEq <250	ditto
305	Lalic 2018	OR	0 comorbidities	ditto
306	Lalic 2018	OR	0 comorbidities	ditto
307	Lalic 2018	OR	0 comorbidities	ditto
308	Lalic 2018	OR	No	ditto
309	Lalic 2018	OR	No	ditto
310	Lalic 2018	OR	No	ditto
311	Lalic 2018	OR	No	ditto
312	Lalic 2018	OR	No	ditto
313	Lalic 2018	OR	No	ditto
314	Lalic 2018	OR	No	ditto
315	Lalic 2018	OR	No	ditto
316	Lalic 2018	OR	No	ditto
317	Lalic 2018	OR	No	ditto
318	Lindestrand 2015	OR	Female	Also 3 mo analysis
319	Lindestrand 2015	OR	<82	ditto
320	Lindestrand 2015	OR	No	ditto
321	Lindestrand 2015	OR	No	ditto
322	Lindestrand 2015	OR	No	ditto
323	Lindestrand 2015	OR	0-1	ditto
324	Lindestrand 2015	OR	No	ditto
325	Lindestrand 2015	OR	No	ditto

Row	Author Year	Metric	Comparator	Note
326	Lindestrand 2015	OR	No	ditto
327	Lindestrand 2015	OR	No	ditto
328	Lindestrand 2015	OR	No	3 mo (6 mo smaller, NS effect)
329	Lo-Ciganic 2019	importance		Importance is a measure of each variable's cumulative contribution toward reducing square error, or heterogeneity within the subset, after the data set is sequentially split according to that variable. Thus, importance reflects a variable's significance in prediction.
330	Lo-Ciganic 2019	importance		ditto
331	Lo-Ciganic 2019	importance		ditto
332	Lo-Ciganic 2019	importance		ditto
333	Lo-Ciganic 2019	importance		ditto
334	Lo-Ciganic 2019	importance		ditto
335	Lo-Ciganic 2019	importance		ditto
336	Loeb 2020	OR	Very low risk	Also (but lower) for lower categories: Low-Regional mets
337	Loeb 2020	OR	CCI 0	Similar for CCI 1, 2
338	Loeb 2020	OR	Married	
339	Loeb 2020	OR	Low	Similar for intermediate education
340	McDermott 2019	OR	66-69	Also 3 mo analysis
341	McDermott 2019	OR	66-69	ditto
342	McDermott 2019	OR	Male	ditto
343	McDermott 2019	OR	White, non-Hispanic	ditto
344	McDermott 2019	OR	Married	ditto
345	McDermott 2019	OR	Metropolitan	ditto
346	McDermott 2019	OR	(various)	ditto
347	McDermott 2019	OR	0	ditto
348	McDermott 2019	OR	0	ditto
349	McDermott 2019	OR	Others	ditto
350	McDermott 2019	OR	No	ditto
351	McDermott 2019	OR	No	ditto
352	McDermott 2019	OR	No	ditto
353	McDermott 2019	OR	Hydrocodone	ditto
354	McDermott 2019	OR	Hydrocodone	ditto
355	McDermott 2019	OR	No	ditto
356	McDermott 2019	OR	No	ditto
357	Musich 2019	OR	Male	
358	Musich 2019	OR	65-69	
359	Musich 2019	OR	65-69	

Row	Author Year	Metric	Comparator	Note
360	Musich 2019	OR	65-69	
361	Musich 2019	OR	65-69	
362	Musich 2019	OR	(continuous)	
363	Musich 2019	OR	Minority high	
364	Musich 2019	OR	Minority high	
365	Musich 2019	OR	Income high	
366	Musich 2019	OR	Income high	
367	Musich 2019	OR	Other (non-urban)	
368	Musich 2019	OR	South	
369	Musich 2019	OR	South	
370	Musich 2019	OR	South	
371	Musich 2019	OR	High coverage	
372	Musich 2019	OR	High coverage	
373	Musich 2019	OR	HCC <0.5	
374	Musich 2019	OR	HCC <0.5	
375	Musich 2019	OR	HCC <0.5	
376	Musich 2019	OR	No long-acting	
377	Musich 2019	OR	No tramadol	
378	Musich 2019	OR	No chronic back pain	
379	Musich 2019	OR	No new back pain	
380	Musich 2019	OR	No TKA	
381	Musich 2019	OR	No Trauma	
382	Musich 2019	OR	No	
383	Musich 2019	OR	No	
384	Musich 2019	OR	No	
385	Musich 2019	OR	No	
386	Musich 2019	OR	No	
387	Musich 2019	OR	No benzo	
388	Musich 2019	OR	No benzo	
389	Musich 2019	OR	No benzo	
390	Musich 2019	OR	No depression	
391	Musich 2019	OR	No depression	
392	Musich 2019	OR	No depression	
393	Musich 2019	OR	No anxiety	
394	Musich 2019	OR	No anxiety	
395	Musich 2019	OR	No anxiety	
396	Namba 2018	OR	(continuous)	Also data for earlier time periods

Row	Author Year	Metric	Comparator	Note
397	Namba 2018	OR	No	ditto
398	Namba 2018	OR	Male	ditto
399	Namba 2018	OR	(continuous)	ditto
400	Namba 2018	OR	White	ditto
401	Namba 2018	OR	White	ditto
402	Namba 2018	OR	White	ditto
403	Namba 2018	OR	(continuous)	ditto
404	Namba 2018	OR	No	ditto
405	Namba 2018	OR	No	ditto
406	Namba 2018	OR	No	ditto
407	Namba 2018	OR	No	ditto
408	Namba 2018	OR	No	ditto
409	Namba 2018	OR	No	ditto
410	Namba 2018	OR	No	ditto
411	Namba 2018	OR	No	ditto
412	Namba 2018	OR	No	ditto
413	Namba 2018	OR	No	ditto
414	Namba 2018	OR	No	ditto
415	Namba 2018	OR	No	ditto
416	Namba 2018	OR	No	ditto
417	Namba 2018	OR	No	ditto
418	Namba 2018	OR	No	ditto
419	Namba 2018	OR	No	ditto
420	Namba 2018	OR	No	ditto
421	Namba 2018	OR	No	ditto
422	Namba 2018	OR	No	ditto
423	Namba 2018	OR	No	ditto
424	Namba 2018	OR	No	ditto
425	Namba 2018	OR	No	ditto
426	Namba 2018	OR	No	ditto
427	Namba 2018	OR	No	ditto
428	Namba 2018	OR	No	ditto
429	Namba 2018	OR	No	ditto
430	Namba 2018	OR	No	ditto
431	Namba 2018	OR	No	ditto
432	Namba 2018	OR	No	ditto
433	Namba 2018	OR	No	ditto

Row	Author Year	Metric	Comparator	Note
434	Namba 2018	OR	No	ditto
435	Namba 2018	OR	No	ditto
436	Namba 2018	OR	No	ditto
437	Namba 2018	OR	No	ditto
438	Namba 2018	OR	No	ditto
439	Namba 2018	OR	No	ditto
440	Namba 2018	OR	No	ditto
441	Namba 2018	OR	No	ditto
442	Namba 2018	OR	No	ditto
443	Nelson 2020	OR	>80	
444	Nelson 2020	OR	>80	
445	Nelson 2020	OR	>80	
446	Nelson 2020	OR	Male	
447	Nelson 2020	OR	Non-Hispanic white	
448	Nelson 2020	OR	Non-Hispanic white	
449	Nelson 2020	OR	Non-Hispanic white	
450	Nelson 2020	OR	Big metropolitan	
451	Nelson 2020	OR	Big metropolitan	
452	Nelson 2020	OR	Big metropolitan	
453	Nelson 2020	OR	Big metropolitan	
454	Nelson 2020	OR	Married	
455	Nelson 2020	OR	<5.66%	
456	Nelson 2020	OR	<5.66%	
457	Nelson 2020	OR	<5.66%	
458	Nelson 2020	OR	<5.24%	
459	Nelson 2020	OR	<5.24%	
460	Nelson 2020	OR	<5.24%	
461	Nelson 2020	OR	Stage I	
462	Nelson 2020	OR	Lobectomy	
463	Nelson 2020	OR	Open surgery	
464	Nelson 2020	OR	No RT	
465	Nelson 2020	OR	No RT	
466	Nelson 2020	OR	No chemotheapy	
467	Nelson 2020	OR	No chemotheapy	
468	Nelson 2020	OR	Well differentiated	
469	Nelson 2020	OR	0	
470	Nelson 2020	OR	0	

Row	Author Year	Metric	Comparator	Note
471	Park 2010	B (linear association, not beta)	(continuous)	
472	Park 2010	B	Female	
473	Park 2010	B	No	
474	Park 2010	B	No	
475	Park 2010	B	(continuous)	
476	Park 2010	B	No	
477	Park 2010	B	(continuous)	
478	Park 2010	B	(continuous)	
479	Park 2010	B	(continuous)	
480	Park 2010	B	(continuous)	
481	Park 2010	B	(continuous)	
482	Park 2010	B	(continuous)	
483	Rao 2018	IRR	Male	Also analyses for prior 3 quarters, separately
484	Rao 2018	IRR	White	ditto
485	Rao 2018	IRR	White	ditto
486	Rao 2018	IRR	White	ditto
487	Rao 2018	IRR	White	ditto
488	Rao 2018	IRR	<30	ditto
489	Rao 2018	IRR	<30	ditto
490	Rao 2018	IRR	1-2	ditto
491	Rao 2018	IRR	0 Rx	ditto
492	Rao 2018	IRR	0 Rx	ditto
493	Rao 2018	IRR	No	ditto
494	Rao 2018	IRR	No	ditto
495	Rao 2018	IRR	No	ditto
496	Rao 2018	IRR	No	ditto
497	Rao 2018	IRR	No	ditto
498	Rao 2018	IRR	No	ditto
499	Rao 2018	IRR	No	ditto
500	Rao 2018	IRR	No	ditto
501	Rao 2018	IRR	No	ditto
502	Rao 2018	IRR	No	ditto
503	Rao 2018	IRR	No	ditto
504	Rao 2018	IRR	No	ditto
505	Rao 2018	IRR	No	ditto
506	Rao 2018	IRR	No	ditto
507	Rao 2018	IRR	No	ditto

Row	Author Year	Metric	Comparator	Note
508	Rao 2018	IRR	No	ditto
509	Rao 2018	IRR	No	ditto
510	Rao 2018	IRR	No	ditto
511	Rao 2018	IRR	No	ditto
512	Rao 2018	IRR	No	ditto
513	Rao 2018	IRR	No	ditto
514	Rao 2018	IRR	No	ditto
515	Rao 2018	IRR	No	ditto
516	Rao 2018	IRR	No	ditto
517	Rao 2018	IRR	No	ditto
518	Rao 2018	IRR	No	ditto
519	Rao 2018	IRR	No	ditto
520	Rao 2018	IRR	No	ditto
521	Rao 2018	IRR	No	ditto
522	Rao 2018	IRR	No	ditto
523	Rao 2018	IRR	No	ditto
524	Rao 2018	IRR	No	ditto
525	Rao 2018	IRR	No	ditto
526	Rao 2018	IRR	No	ditto
527	Rao 2018	IRR	No	ditto
528	Rao 2018	IRR	No	ditto
529	Rao 2018	IRR	No	ditto
530	Rao 2018	IRR	No	ditto
531	Rao 2018	IRR	No	ditto
532	Santosa 2020	OR	No	
533	Santosa 2020	OR	No	
534	Santosa 2020	OR	No	
535	Santosa 2020	OR	No	
536	Santosa 2020	OR	Minor surgery	
537	Santosa 2020	OR	Rx only filled within 14 days after surgical discharge	
538	Santosa 2020	OR	OMEs < 75th percentile	
539	Santosa 2020	OR	No refill	
540	Santosa 2020	OR	No refill	
541	Santosa 2020	OR	Age 65-69	
542	Santosa 2020	OR	Age 65-69	
543	Santosa 2020	OR	Age 65-69	

Row	Author Year	Metric	Comparator	Note
544	Santosa 2020	OR	Age 65-69	
545	Santosa 2020	OR	Male	
546	Santosa 2020	OR	White	
547	Santosa 2020	OR	White	
548	Santosa 2020	OR	White	
549	Santosa 2020	OR	Nonmetropolitan	
550	Santosa 2020	OR	East north central	
551	Santosa 2020	OR	East north central	
552	Santosa 2020	OR	East north central	
553	Santosa 2020	OR	East north central	
554	Santosa 2020	OR	East north central	
555	Santosa 2020	OR	East north central	
556	Santosa 2020	OR	East north central	
557	Santosa 2020	OR	East north central	
558	Santosa 2020	OR	No	
559	Santosa 2020	OR	CCI 0	
560	Santosa 2020	OR	CCI 0	
561	Santosa 2020	OR	CCI 0	
562	Santosa 2020	OR	No	
563	Santosa 2020	OR	No	
564	Santosa 2020	OR	No	
565	Santosa 2020	OR	No	
566	Santosa 2020	OR	No	
567	Santosa 2020	OR	No	
568	Santosa 2020	OR	No	
569	Santosa 2020	OR	No	
570	Santosa 2020	OR	No	
571	Santosa 2020	OR	No	
572	Santosa 2020	OR	No	
573	Santosa 2020	OR	No	
574	Schepis 2019	OR	No past-year use	
575	Schepis 2019	OR	No	
576	Shah 2019	OR	(continuous)	All
577	Shah 2019	OR	65-74	All
578	Shah 2019	OR	65-74	All
579	Shah 2019	OR	Male	All
580	Shah 2019	OR	White	All

Row	Author Year	Metric	Comparator	Note
581	Shah 2019	OR	White	All
582	Shah 2019	OR	White	All
583	Shah 2019	OR	Metropolitan	All
584	Shah 2019	OR	Metropolitan	All
585	Shah 2019	OR	Prostate cancer	All
586	Shah 2019	OR	Prostate cancer	All
587	Shah 2019	OR	Prostate cancer	All
588	Shah 2019	OR	No	All
589	Shah 2019	OR	No	All
590	Shah 2019	OR	No	All
591	Shah 2019	OR	No	All
592	Shah 2019	OR	No	All
593	Shah 2019	OR	No	All
594	Shah 2019	OR	(continuous)	Opioid naïve
595	Shah 2019	OR	65-74	Opioid naïve
596	Shah 2019	OR	65-74	Opioid naïve
597	Shah 2019	OR	Male	Opioid naïve
598	Shah 2019	OR	White	Opioid naïve
599	Shah 2019	OR	White	Opioid naïve
600	Shah 2019	OR	White	Opioid naïve
601	Shah 2019	OR	Metropolitan	Opioid naïve
602	Shah 2019	OR	Metropolitan	Opioid naïve
603	Shah 2019	OR	Prostate cancer	Opioid naïve
604	Shah 2019	OR	Prostate cancer	Opioid naïve
605	Shah 2019	OR	Prostate cancer	Opioid naïve
606	Shah 2019	OR	No	Opioid naïve
607	Shah 2019	OR	No	Opioid naïve
608	Shah 2019	OR	No	Opioid naïve
609	Shah 2019	OR	No	Opioid naïve
610	Shah 2019	OR	No	Opioid naïve
611	Suda 2017	OR	Male	
612	Suda 2017	OR	66-70	
613	Suda 2017	OR	66-70	
614	Suda 2017	OR	66-70	
615	Suda 2017	OR	66-70	
616	Suda 2017	OR	66-70	
617	Suda 2017	OR	White	

Row	Author Year	Metric	Comparator	Note
618	Suda 2017	OR	Hispanic	
619	Suda 2017	OR	Full copay	
620	Suda 2017	OR	Full copay	
621	Suda 2017	OR	>5 miles	
622	Suda 2017	OR	>5 miles	
623	Suda 2017	OR	>5 miles	
624	Suda 2017	OR	>5 miles	
625	Suda 2017	OR	(continuous)	inconsistent across variables
626	Suda 2017	OR	(continuous)	Poorly defined, inconsistent across variables
627	Suda 2017	OR	Urban	
628	Suda 2017	OR	(continuous)	HCC=risk-adjustment model originally designed to estimate future health care costs for patients.
629	Suda 2017	OR	No	
630	Suda 2017	OR	No	
631	Suda 2017	OR	No	
632	Suda 2017	OR	No	
633	Suda 2017	OR	No	
634	Suda 2017	OR	No	
635	Suda 2017	OR	(continuous)	
636	Suda 2017	OR	(continuous)	
637	Suda 2017	OR	(continuous)	
638	Taipale 2019	HR	Non-user	
639	Taipale 2019	HR	0 days (implied)	
640	Taipale 2019	HR	0 days (implied)	
641	Taipale 2019	HR	0 days (implied)	
642	Taipale 2019	HR	0 days (implied)	
643	Taipale 2019	HR	No opioid (implied)	
644	Taipale 2019	HR	No opioid (implied)	
645	Taipale 2019	HR	No opioid (implied)	
646	Vozoris 2016	HR	No use	
647	Vozoris 2016	HR	No use	
648	Vozoris 2016	HR	No use	
649	Vozoris 2016	HR	No use	
650	Vozoris 2016	HR	No use	
651	Vozoris 2016	HR	No use	
652	Zeng 2019	HR	Other analgesic	1 of multiple comparisons
653	Zoorob 2018	OR	(continuous)	Any overdose of (apparently) any entity. Other analyses reported.

Row	Author Year	Metric	Comparator	Note
654	Zoorob 2018	OR	(continuous)	ditto
655	Zoorob 2018	OR	(continuous)	ditto
656	Zoorob 2018	OR	(continuous)	ditto
657	Zoorob 2018	OR	(continuous)	ditto
658	Zoorob 2018	OR	(continuous)	ditto
659	Zoorob 2018	OR	(continuous)	ditto
660	Zoorob 2018	OR	Non-rural	ditto
661	Zoorob 2018	OR	(continuous)	ditto

Abbreviations: AD = Alzheimer disease, ADL = activities of daily living, AIDS = acquired immunodeficiency syndrome, ASA = American Society of Anesthesiology (grade), AUD = alcohol use disorder, B = beta coefficient, BMI = body mass index, CAGE = alcohol use disorder prediction tool, COPD = chronic obstructive pulmonary disease, ED = emergency department, ER = emergency room, HR = hazard ratio, Hx = history of, ICU = intensive care unit, IRR = incidence rate ratio, MEq = morphine equivalents, MME = mean morphine equivalents, NS = nonsignificant, NSAID = nonsteroidal anti-inflammatory drug, OR = odds ratio, PTSD = posttraumatic stress disorder, QoL = quality of life, RR = risk ratio, RRR = relative risk ratio, Rx = prescription, SES = socioeconomic status, SUD = substance use disorder, TKA = total knee arthroplasty, Tx = treatment, VA = Veterans Administration.

Table D-4. Intervention Studies

Author PMID	GQ 3 Intervention	GQ 3 Intent/Goal of Intervention
Beaudoin 27426210	Screening Question / Questionnaire (e.g. that identify possible misuse by having older adults answer a series of questions)	Intervention helps providers identify opioid misuse or opioid use disorder in older adults
Chang 31187888	Motivational interviewing training	Manage prescription opioid abuse among older adults
Chen 31314748	Opioid safety initiative	Reduce opioid prescriptions while maintaining pain control
Cheng 31234786	Prediction Tool / Model	Intervention helps providers identify opioid misuse or opioid use disorder in older adults
Darchuk 20735746	Non-Pharmacologic Treatments (e.g. Cognitive Behavioral Therapy and Related Interventions) for Pain Control)	Discontinuation of all opioid and simple analgesics taken for relief of chronic pain
Draper 2015 25247846	ASSIST (Alcohol, Smoking and Substance Involvement Screening Test)	Screening
Gugelmann 2013 23906621	Bundle of educational modalities	Decrease opioid discharge pack use in patients treated and released from the ED
Henderson 26056833	Prediction Tool / Model	Intervention helps providers identify opioid misuse or opioid use disorder in older adults
Moyo 28498498, 31372990	Prescription drug monitoring program	Reduce opioid prescriptions (state-wide)
Park 21143370	Prediction Tool / Model	Intervention helps providers identify opioid misuse or opioid use disorder in older adults
Pasquale 2017 29199396	Provision of patient information; Educational materials	Reduce pain- and opioid-related outcomes
Rose 2016 26431852	Patient education pamphlet	Safe opioid storage, opioid weaning, and opioid disposal; and post-operative opioid cessation
Schaffer 29581162	Introduction of tamper resistant formulation	Intervention helps providers reduce the risk of adverse events
Tiet 30947051	Screening Question / Questionnaire (e.g. that identify possible misuse by having older adults answer a series of questions)	Intervention helps providers identify opioid misuse or opioid use disorder in older adults
Vicentini 31810456	Access to nonopioid	Free acetaminophen prescription
Yarbrough 28101955	Quality Improvement Initiatives / Implementation Strategies to Promoted Evidence-based Care	Intervention helps providers reduce the risk of adverse events

Abbreviation: GQ = Guiding Question, PMID = PubMed identifier.

Table D-5. Baseline data for included studies

Author PMID	Mean Age	N >=60	N >=65	N >=75	Special Population	% Female	% White	Opioid Use Type
Al Dabbagh 26707940	75	Not an analyzed cohort	Not an analyzed cohort	Subgroup (explicit) only	No	56	NR	Appropriate prescription opioid use
Alam 22412106	76	All of study population	.	Not an analyzed cohort	No	38	NR	Appropriate prescription opioid use
Beaudoin 27426210	60	Subgroup (explicit) only	.	Unclear	No	59	80	Misuse, prescription opioid, but not recreational (e.g., taking more than prescribed)
Cancienne 28887020	NR	Subgroup (explicit) only	Subgroup (explicit) only	Subgroup (explicit) only		64.5	NR	Several
Carey 29800019	NR	Not an analyzed cohort	Subgroup (explicit) only	Not an analyzed cohort	Medicare	56.8-66.0	72.5-85.3	Several
Carter 30863796	NR	All of study population	All of study population	Subgroup (explicit) only	No	58.6	NR	Several
Chang 2019 31187888	NR	Unclear	Unclear	Unclear	No	NR	NR	Misuse, prescription opioid, but not recreational (e.g., taking more than prescribed)
Chen 2019 31314748	64	Unclear	Unclear	Unclear	Veterans	6.4	78.4	Appropriate prescription opioid use (post-surgical)
Cheng 31234786	78.5	Not an analyzed cohort	All of study population	Not an analyzed cohort	No	66	NR	Misuse, prescription opioid, recreational (e.g, taking without a medical indication; snorting / injecting)
Choi 28699829	63	Unclear	Subgroup (explicit) only	Not an analyzed cohort	No	53	75	Several
Choi 30585135	NR	All of study population	Subgroup (explicit) only	Not an analyzed cohort	No	NR	NR	Several

Author PMID	Mean Age	N >=60	N >=65	N >=75	Special Population	% Female	% White	Opioid Use Type
Cochran 28489491	NR	Not an analyzed cohort	Subgroup (explicit) only	Not an analyzed cohort	No	66.7	NR	Misuse, prescription opioid, but not recreational (e.g., taking more than prescribed)
Curtis 28635179	76	Not an analyzed cohort	All of study population	Not an analyzed cohort	Medicare	76	84	Several
Daoust 28767563	79.3	Not an analyzed cohort	All of study population	Not an analyzed cohort	No	69.2	NR	Misuse, prescription opioid, but not recreational (e.g., taking more than prescribed)
Darchuk 20735746	66.5	Subgroup (explicit) only	Not an analyzed cohort	Not an analyzed cohort	No	50	76	Appropriate prescription opioid use
Draper 25247846	81.9	All of study population	Unclear	Unclear	No	63.3	NR	Several
Gold 27564407	NR	Not an analyzed cohort (>=75)	Not an analyzed cohort (>=75)	All of study population	No	58.1	87.3	Misuse, prescription opioid, recreational (e.g, taking without a medical indication; snorting / injecting)
Grigoras 29159797	NR	Not an analyzed cohort	Subgroup (explicit) only	Not an analyzed cohort	Medicare	NR	NR	Appropriate prescription opioid use
Gugelmann 23906621	37.5	Unclear	Subgroup (explicit) only	Not an analyzed cohort	No	62	32	Appropriate prescription opioid use
Hadlandsmyth 28927564	66	Subgroup (explicit) only	Subgroup (explicit) only	Subgroup (explicit) only	Veterans	NR	NR	Appropriate prescription opioid use
Hamina 28092324	79.9	Not an analyzed cohort	Not an analyzed cohort	Not an analyzed cohort	No	NR	NR	Appropriate prescription opioid use
Henderson 26056833	75	Not an analyzed cohort (>=75)	Not an analyzed cohort (>=75)	All of study population	No	58	100	Several
Hoffman 28531306	67	Unclear	Unclear	Unclear	No	47.2	NR	Appropriate prescription opioid use

Author PMID	Mean Age	N >=60	N >=65	N >=75	Special Population	% Female	% White	Opioid Use Type
Inacio 27130165	80	Not an analyzed cohort	Not an analyzed cohort	Not an analyzed cohort	No	51.3	NR	Appropriate prescription opioid use
Jain 29561298	65.6	Unclear	Unclear	Unclear	No	58.5	75.1	Appropriate prescription opioid use
Jeffery 28967517	73	Unclear	Unclear	Unclear	Medicare	57.2	74.7	Appropriate prescription opioid use
Jena 24553363	68.5	Unclear	Subgroup (explicit) only	Subgroup (explicit) only	Medicare	63.3	81.1	Appropriate prescription opioid use
Karttunen 30370943	80	Not an analyzed cohort	Not an analyzed cohort	Not an analyzed cohort	No	70	NR	Appropriate prescription opioid use
Kuo 26522794	NR	Not an analyzed cohort (>=75)	Not an analyzed cohort (>=75)	All of study population	Medicare	67.2	81.8	Appropriate prescription opioid use
Lalic 29451672	NR	Not an analyzed cohort	Subgroup (explicit) only	Subgroup (explicit) only	No	NR	NR	Appropriate prescription opioid use
Lindestrand 25952252	80	Not an analyzed cohort	Not an analyzed cohort	Not an analyzed cohort	No	72	NR	Several
Lo-Ciganic 30901048	68	Not an analyzed cohort	Not an analyzed cohort	Not an analyzed cohort	Medicare	63	82	Misuse, prescription opioid, but not recreational (e.g., taking more than prescribed)
McDermott 30396321	NR	Not an analyzed cohort (>=65)	All of study population	Subgroup (explicit) only	Medicare	NR	NR	Appropriate prescription opioid use
Moyo 28498498, 31372990	71.4	Not an analyzed cohort	Not an analyzed cohort	Not an analyzed cohort	Medicare	62	78.3	Appropriate prescription opioid use
Namba 29753617	67	Not an analyzed cohort (>=65)	All of study population	Not an analyzed cohort	No	62.9	65.9	Several

Author PMID	Mean Age	N >=60	N >=65	N >=75	Special Population	% Female	% White	Opioid Use Type
Park 20664342	72.8	Not an analyzed cohort	All of study population	Not an analyzed cohort	No	31.3	51.5	Misuse, prescription opioid, but not recreational (e.g., taking more than prescribed)
Park 21143370	72.7	Not an analyzed cohort	All of study population	Not an analyzed cohort	No	29.3	50.7	Misuse, prescription opioid, but not recreational (e.g., taking more than prescribed)
Pasquale 29199396	NR	Not an analyzed cohort	All of study population	Not an analyzed cohort	Medicare	NR	NR	Several
Rao 29891412	NR	Subgroup (explicit) only	Not an analyzed cohort	Not an analyzed cohort	No	48.1	80.5	Appropriate prescription opioid use
Rose 26431852	63	Not an analyzed cohort	Not an analyzed cohort	Not an analyzed cohort	No	58	NR	Appropriate prescription opioid use
Schaffer 29581162	NR	Not an analyzed cohort	Subgroup (explicit) only	Subgroup (explicit) only	No	NR	NR	Misuse, prescription opioid, but not recreational (e.g., taking more than prescribed)
Schepis 30328160	NR	Not an analyzed cohort	Subgroup (explicit) only	Not an analyzed cohort	No	NR	NR	Misuse, prescription opioid, recreational (e.g, taking without a medical indication; snorting / injecting)
Shah 31026356	NR	Not an analyzed cohort (>=65)	All of study population	Not an analyzed cohort	Medicare	56	74	Misuse, prescription opioid, but not recreational (e.g., taking more than prescribed)
Suda 28408172	78	Not an analyzed cohort	All of study population	Not an analyzed cohort	Veterans	22.3	NR	Appropriate prescription opioid use
Taipale 30325873	83	Not an analyzed cohort	Subgroup (explicit) only	Subgroup (explicit) only	No	66.7	NR	Appropriate prescription opioid use
Tiet 2019 30947051	62	Not an analyzed cohort	Not an analyzed cohort	Not an analyzed cohort	Veterans	5	54.7	Opioid use disorder

Author PMID	Mean Age	N >=60	N >=65	N >=75	Special Population	% Female	% White	Opioid Use Type
Vicentini 2019 31810456	79	All of study population	All of study population	Not an analyzed cohort	No	79.3	NR	Appropriate prescription opioid use
Vozoris 27418553	77	Not an analyzed cohort	Subgroup (explicit) only	Not an analyzed cohort	No	47		Appropriate prescription opioid use
Yarbrough 28101955	NR	Not an analyzed cohort	Not an analyzed cohort	Not an analyzed cohort	Medicare	NR	NR	Unclear/Undefined/Other
Zeng 30860559	70.1	Not an analyzed cohort	Not an analyzed cohort	Not an analyzed cohort	No	63	NR	Appropriate prescription opioid use
Zoorob 29537112	>=65	Not an analyzed cohort	All of study population	Not an analyzed cohort	Medicare	NR	NR	Appropriate prescription opioid use

Abbreviation: PMID = PubMed identifier

Table D-6. Study design data of included studies

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Al Dabbagh 26707940	Single Group	Retrospective	Cross-Sectional	Sweden	Unclear/Undefined	1471	2005, 2008	Chronic pain	non-cancer pain	Secondary musculoskeletal pain (pain in bones, joint and tendons arising from an underlying disease classified elsewhere. It can be due to persistent inflammation, associated with structural changes or caused by altered biomechanical function due to diseases of the nervous system)

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Alam 22412106	Non-Randomized Comparative Study	Retrospective	Longitudinal	Canada	Outpatient / community / clinics	391,139	1997, 2008	Acute pain	Low-pain ambulatory operations (cataract surgery; laparoscopic cholecystectomy; transurethral resection of the prostate; varicose vein stripping surgery)	.
Beaudoin 27426210	Single Group	Retrospective	Cross-Sectional	USA	Emergency department / observation stay	112	2013, 2014	Any pain	Any	.
Cancienne 28887020	Non-Randomized Comparative Study	Retrospective	Cross-Sectional	USA	Several or Transitions of Care	113337	2007, 2015	Unclear/ Undefined	Total knee arthroplasty	.
Carey 29800019	Single Group	Retrospective	Cross-Sectional	USA	Unclear/Undefined	627391	2008, 2012	Unclear/ Undefined	Not specified	Unclear/Undefined/ Not Specified
Carter 30863796	Single Group	Retrospective	Cross-Sectional	USA	Emergency department / observation stay	28167	2006, 2014	Any pain	Not specified	.

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Chang 31187888	Single Group	Prospective	Cross-Sectional	USA	Unclear / Undefined	31	2019	Chronic pain	Non-cancer	Unclear/Undefined/Not Specified
Chen 2019 31314748	Pre-post	Retrospective	Longitudinal	USA	Outpatient	60,046	2010, 2015	Post-surgical	Total knee arthroplasty	Unclear/Undefined/Not Specified
Cheng 31234786	Single Group	Prospective	Cross-Sectional	Norway	Outpatient / community / clinics	100	2017, 2018	Unclear/ Undefined	Not specified	Unclear/Undefined/Not Specified
Choi 28699829	Single Group	Retrospective	Cross-Sectional	USA	Unclear/Undefined	14,715	2012, 2013	Unclear/ Undefined	Not specified	Unclear/Undefined/Not Specified
Choi 30585135	Single Group	Retrospective	Cross-Sectional	USA	Emergency department / observation stay	17608	2015, 2016	Unclear/ Undefined	Not specified	Unclear/Undefined/Not Specified
Cochran 28489491	Single Group	Prospective	Cross-Sectional	USA	Outpatient / community / clinics	36	NR	Unclear/ Undefined	Not specified	Unclear/Undefined/Not Specified
Curtis 28635179	Single Group	Retrospective	Cross-Sectional	USA	Unclear/Undefined	70,929	2006, 2014	Unclear/ Undefined	Rheumatoid Arthritis	Unclear/Undefined/Not Specified

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Daoust 28767563	Single Group	Retrospective	Longitudinal	Canada	Outpatient / community / clinics	39833	2004, 2014	Unclear/ Undefined	Post trauma/surgery	Postsurgical or post-traumatic pain (pain that develops or increases in intensity after a tissue trauma (surgical or accidental) and persists beyond three months)
Darchuk 20735746	Single Group	Prospective	Longitudinal	USA	Outpatient / community / clinics	78	2004, 2006	Chronic pain	Non-cancer	.
Draper 25247846	Single Group	Retrospective	Cross-Sectional	Australia	Several or Transitions of Care	210	2011, 2012	Any pain	Not specific	Unclear/Undefined/ Not Specified
Gold 27564407	Single Group	Retrospective	Cross-Sectional	USA	Unclear/Undefined	725	2012	Does not address pain	.	.
Grigoras 29159797	Single Group	Retrospective	Cross-Sectional	USA	Several or Transitions of Care	46,665,037	2013, 2014	Unclear/ Undefined	Not Specified	Unclear/Undefined/ Not Specified
Gugelmann 23906621	Single Group	Prospective	Longitudinal	USA	Emergency department / observation stay	1360	2011, 2012	Chronic pain	Multiple	.

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Hadlandsmyth 28927564	Single Group	Retrospective	Longitudinal	USA	Several or Transitions of Care	5089	2013, 2015	.	.	.
Hamina 28092324	Non-Randomized Comparative Study	Prospective	Longitudinal	Finland	Several or Transitions of Care	141,436	NR	Chronic pain	nonmalignant pain	Unclear/Undefined/ Not Specified
Henderson 26056833	Single Group	Prospective	Cross-Sectional	USA	Emergency department / observation stay	88	2011	Any pain	Not Specified (not cancer pain)	Unclear/Undefined/ Not Specified
Hoffman 28531306	Non-Randomized Comparative Study	Retrospective	Cross-Sectional	USA	Unclear/Undefined	17327	2006, 2010	Chronic pain	Polyneuropathy	Neuropathic pain (pain caused by a lesion or disease of the somatosensory nervous system. Peripheral and central neuropathic pain are classified here)

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Inacio 27130165	Single Group	Retrospective	Longitudinal	Australia	Inpatient / hospital	9,525	2001, 2012	Chronic pain	Total knee arthroplasty	Secondary musculoskeletal pain (pain in bones, joint and tendons arising from an underlying disease classified elsewhere. It can be due to persistent inflammation, associated with structural changes or caused by altered biomechanical function due to diseases of the nervous system)

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Jain 29561298	Single Group	Retrospective	Longitudinal	USA	Several or Transitions of Care	24,610	2007, 2015	Unclear/ Undefined	Posterior lumbar fusion surgery	Postsurgical or post-traumatic pain (pain that develops or increases in intensity after a tissue trauma (surgical or accidental) and persists beyond three months)
Jeffery 28967517	Non-Randomized Comparative Study	Retrospective	Cross-Sectional	USA	Emergency department / observation stay	10,078,948	2009, 2015	Unclear/ Undefined	Not specified	Unclear/Undefined/ Not Specified
Jena 24553363	Single Group	Retrospective	Cross-Sectional	USA	Outpatient / community / clinics	808,355	2010	Unclear/ Undefined	Not specified	Unclear/Undefined/ Not Specified
Karttunen 30370943	Non-Randomized Comparative Study	Retrospective	Cross-Sectional	Finland	Unclear/Undefined	6784	2005, 2011	Does not address pain	Not specified	Unclear/Undefined/ Not Specified
Kuo 26522794	Single Group	Retrospective	Longitudinal	USA	Several or Transitions of Care	515,196	2007, 2012	Does not address pain	.	.

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Lalic 29451672	Single Group	Prospective	Longitudinal	Australia	Unclear/Undefined	94,907	2013, 2015	Does not address pain	.	.
Lindestrand 25952252	Single Group	Retrospective	Cross-Sectional	USA	Unclear/Undefined	410	NR	Unclear/ Undefined	Not specified	Unclear/Undefined/ Not Specified
Lo-Ciganic 30901048	Single Group	Retrospective	Cross-Sectional	USA	.	186 686	January 1, 2011, and December 31, 2015	Unclear/ Undefined	Multiple	.
McDermott 30396321	Non-Randomized Comparative Study	Retrospective	Cross-Sectional	USA	Unclear/Undefined	811	2008, 2011	Chronic pain	Oral and Oropharyngeal cancer	Unclear/Undefined/ Not Specified
Moyo 28498498, 31372990	Non-Randomized Comparative Study	Retrospective	Longitudinal	US	Outpatient / community / clinics	310105	2007, 2012	Does not address pain	Not specified	Unclear/Undefined/ Not Specified

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Namba 29753617	Single Group	Retrospective	Longitudinal	USA	Several or Transitions of Care	23, 726	2008, 2011	Chronic pain	Total knee arthroplasty	Secondary musculoskeletal pain (pain in bones, joint and tendons arising from an underlying disease classified elsewhere. It can be due to persistent inflammation, associated with structural changes or caused by altered biomechanical function due to diseases of the nervous system)
Park 20664342	Single Group	Prospective	Longitudinal	US	Outpatient / community / clinics	163	2008, 2009	Chronic pain	Not specified	Unclear/Undefined/ Not Specified

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Park 21143370	Single Group	Prospective	Longitudinal	US	Outpatient / community / clinics	150	NR	Chronic pain	arthritis/joint problems, back problems, type II diabetes, headaches, dental problems, heart disease, cancer, osteoporosis, or stroke	Unclear/Undefined/ Not Specified
Pasquale 29199396	Randomized Comparative Study	Prospective	Longitudinal	US	Several or Transitions of Care	6744	2012, 2014	Several	Not specified	Unclear/Undefined/ Not Specified

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Rao 29891412	Non-Randomized Comparative Study	Prospective	Longitudinal	USA	Unclear/Undefined	3570	2008, 2014	Chronic pain	Shouler Arthroplasty	Secondary musculoskeletal pain (pain in bones, joint and tendons arising from an underlying disease classified elsewhere. It can be due to persistent inflammation, associated with structural changes or caused by altered biomechanical function due to diseases of the nervous system)
Rose 26431852	Non-Randomized Comparative Study	Prospective	Longitudinal	Canada	Inpatient / hospital	172	2014, 2014	Acute pain		

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Schaffer 29581162	Non-Randomized Comparative Study	Prospective	Longitudinal	Australia	Outpatient / community / clinics	5055	2013, 2014	Unclear/ Undefined	Not specified	Unclear/Undefined/ Not Specified
Schepis 30328160	Single Group	Retrospective	Cross-Sectional	US	Outpatient / community / clinics	17608	2015, 2016	Unclear/ Undefined	Not specified	Unclear/Undefined/ Not Specified
Shah 31026356	Non-Randomized Comparative Study	Retrospective	Longitudinal	US	Unclear/Undefined	63815	1995, 2014	Unclear/ Undefined	Cancer pain	Cancer-related pain (pain that is due to cancer or its treatment, such as chemotherapy)
Suda 28408172	Non-Randomized Comparative Study	Retrospective	Cross-Sectional	US	Outpatient / community / clinics	129106	2005, 2009	Unclear/ Undefined	Not specified	Unclear/Undefined/ Not Specified
Taipale 30325873	Single Group	Retrospective	Cross-Sectional	Finland	Outpatient / community / clinics	4750	2005, 2011	Unclear/ Undefined	Alzheimers	Unclear/Undefined/ Not Specified
Tiet 2019 30947051	Single Group	Prospective	Longitudinal	US	Outpatient / community / clinics	1283	2014, 2014	Does not address pain	Not Specified	Unclear/Undefined/ Not Specified
Vicentini 2019 31810456	Cluster randomized	Prospective	Longitudinal	Italy	Outpatient / community / clinics	117	2012, 2013	Chronic pain	Osteoarthritis	Unclear/Undefined/ Not Specified

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Vozoris 27418553	Non-Randomized Comparative Study	Retrospective	Cross-Sectional	Canada	Several or Transitions of Care	89327	2007, 2012	Does not address pain	COPD	Unclear/Undefined/ Not Specified
Yarbrough 28101955	Non-Randomized Comparative Study	Retrospective	Cross-Sectional	US	Unclear/Undefined	6920	2010, 2013	Unclear/ Undefined	Not Specified	Unclear/Undefined/ Not Specified

Author PMID	Design	Conduct	Temporality	Country	Setting	N Older Adults Analyzed	Enrollment/ Data Years	Pain Time Course	Pain Condition	Pain Category
Zeng 30860559	Non-Randomized Comparative Study	Retrospective	Longitudinal	UK	Outpatient / community / clinics	88,902	2000, 2015	Any pain	osteoarthritis	Secondary musculoskeletal pain (pain in bones, joint and tendons arising from an underlying disease classified elsewhere. It can be due to persistent inflammation, associated with structural changes or caused by altered biomechanical function due to diseases of the nervous system)
Zoorob 29537112	Single Group	Prospective	Cross-Sectional	US	Outpatient / community / clinics	NR (county level data)	2013, 2015	Unclear/ Undefined	Not Specified	Unclear/Undefined/ Not Specified

Abbreviation: PMID = PubMed identifier.

Appendix E. Rejected Articles

Table E-1. Rejected studies: Did not meet principal eligibility criteria

Author PMID	Rejection Reason	Mean age
Sumner 26383533	Age <50 (mean or median) and no subgroup >=60	
Banerjee 27552496	Age <50 (mean or median) and no subgroup >=60	49.7
Banerjee 31145217	Age <50 (mean or median) and no subgroup >=60	NR
Bates 27770163	Age <50 (mean or median) and no subgroup >=60	49.9
Becker 18222051	Age <50 (mean or median) and no subgroup >=60	
Bedard 29958754	Age <50 (mean or median) and no subgroup >=60	NR
Bedard 29452972	Age <50 (mean or median) and no subgroup >=60	NR
Bohnert 26807540	Age <50 (mean or median) and no subgroup >=60	
Choi 31071494	Age <50 (mean or median) and no subgroup >=60	
Cicero 21831562	Age <50 (mean or median) and no subgroup >=60	25-34
Curtis 16704515	Age <50 (mean or median) and no subgroup >=60	38
Darke 19489991	Age <50 (mean or median) and no subgroup >=60	29.3
Deyo 23459134	Age <50 (mean or median) and no subgroup >=60	48.6
Dursteler-MacFarland 21592331	Age <50 (mean or median) and no subgroup >=60	38
Edelman 27186715	Age <50 (mean or median) and no subgroup >=60	48
Gilbert 20309384	Age <50 (mean or median) and no subgroup >=60	48.7
Gotthardt 26747613	Age <50 (mean or median) and no subgroup >=60	44
Johnson 17682079	Age <50 (mean or median) and no subgroup >=60	39.3
Kaasalainen 103802641	Age <50 (mean or median) and no subgroup >=60	45
Mancino 20465373	Age <50 (mean or median) and no subgroup >=60	48.2
McHugh 2016-41984-001	Age <50 (mean or median) and no subgroup >=60	28.4
Merlo 26971079	Age <50 (mean or median) and no subgroup >=60	43
Ogle 22925507	Age <50 (mean or median) and no subgroup >=60	41.8
Oliva 26675643	Age <50 (mean or median) and no subgroup >=60	48.7
Pope 27353833	Age <50 (mean or median) and no subgroup >=60	49
Santora 17935930	Age <50 (mean or median) and no subgroup >=60	42
Scherrer 2016-08181-001	Age <50 (mean or median) and no subgroup >=60	49
Shi 21951787	Age <50 (mean or median) and no subgroup >=60	49
Song 29200349	Age <50 (mean or median) and no subgroup >=60	47.6
Summers 129418933	Age <50 (mean or median) and no subgroup >=60	46
Trafton 16562404	Age <50 (mean or median) and no subgroup >=60	49
Tye 28187073	Age <50 (mean or median) and no subgroup >=60	49
White 19789432	Age <50 (mean or median) and no subgroup >=60	
Wichmann 22505303	Age <50 (mean or median) and no subgroup >=60	34.2
Ahn 26360141	Age <50 (mean or median) and no subgroup >=60	NR
Wu 17000351	Age 50-59.9 (mean or median) and no subgroup >=60	53
Alemi 30283729	Age 50-59.9 (mean or median) and no subgroup >=60	59.45
Annaheim 28835980	Age 50-59.9 (mean or median) and no subgroup >=60	58.8

Author PMID	Rejection Reason	Mean age
Armaghani 25417827	Age 50-59.9 (mean or median) and no subgroup >=60	57
Back 19542794	Age 50-59.9 (mean or median) and no subgroup >=60	51.6
Barnett 31144281	Age 50-59.9 (mean or median) and no subgroup >=60	58.4
Barry 21354703	Age 50-59.9 (mean or median) and no subgroup >=60	52
Barry 30176548	Age 50-59.9 (mean or median) and no subgroup >=60	52
Bell 26684868	Age 50-59.9 (mean or median) and no subgroup >=60	
Brown 22320029	Age 50-59.9 (mean or median) and no subgroup >=60	NR
Campbell 29410132	Age 50-59.9 (mean or median) and no subgroup >=60	51.8
Campbell 20724688	Age 50-59.9 (mean or median) and no subgroup >=60	
Carroll 22729963	Age 50-59.9 (mean or median) and no subgroup >=60	58
Carroll 2016-04174-019	Age 50-59.9 (mean or median) and no subgroup >=60	58.1
Chang 25159493	Age 50-59.9 (mean or median) and no subgroup >=60	59.1
Choung 19367263	Age 50-59.9 (mean or median) and no subgroup >=60	56
Compton 18508231	Age 50-59.9 (mean or median) and no subgroup >=60	53
Conner 2010-02907-004	Age 50-59.9 (mean or median) and no subgroup >=60	NR, but in 50s
de Sola 29248566	Age 50-59.9 (mean or median) and no subgroup >=60	50.5
Demidenko 28807135	Age 50-59.9 (mean or median) and no subgroup >=60	55
Dobscha 23269280	Age 50-59.9 (mean or median) and no subgroup >=60	56.8
Duensing 20429822	Age 50-59.9 (mean or median) and no subgroup >=60	53
Edelman 30615036	Age 50-59.9 (mean or median) and no subgroup >=60	55
Engel 25202832	Age 50-59.9 (mean or median) and no subgroup >=60	56.8
Fareed 19461397	Age 50-59.9 (mean or median) and no subgroup >=60	55.6
Fareed 104694982	Age 50-59.9 (mean or median) and no subgroup >=60	52
Frank 25716075	Age 50-59.9 (mean or median) and no subgroup >=60	58.5
Gaither 30122319	Age 50-59.9 (mean or median) and no subgroup >=60	51
Garcia 28807366	Age 50-59.9 (mean or median) and no subgroup >=60	57
Gressler 29189516	Age 50-59.9 (mean or median) and no subgroup >=60	57.3
Hansen 26899477	Age 50-59.9 (mean or median) and no subgroup >=60	51.6
Hartel 16838244	Age 50-59.9 (mean or median) and no subgroup >=60	NR
Hausmann 23273103	Age 50-59.9 (mean or median) and no subgroup >=60	57
Hser 15669446	Age 50-59.9 (mean or median) and no subgroup >=60	58.4
Hser 11343531	Age 50-59.9 (mean or median) and no subgroup >=60	57.4
Ives 16595013	Age 50-59.9 (mean or median) and no subgroup >=60	52
Kim 27869630	Age 50-59.9 (mean or median) and no subgroup >=60	56
Lane 29044798	Age 50-59.9 (mean or median) and no subgroup >=60	56.3
Larney 25575652	Age 50-59.9 (mean or median) and no subgroup >=60	55
Liebschutz 28715535	Age 50-59.9 (mean or median) and no subgroup >=60	54.7
Lintzeris 26498741	Age 50-59.9 (mean or median) and no subgroup >=60	55
Loftus 20693876	Age 50-59.9 (mean or median) and no subgroup >=60	51.5
Lofwall 15857727	Age 50-59.9 (mean or median) and no subgroup >=60	53.9
Mahowald 15641058	Age 50-59.9 (mean or median) and no subgroup >=60	59
Manhapra 26429726	Age 50-59.9 (mean or median) and no subgroup >=60	52.73

Author PMID	Rejection Reason	Mean age
Marienfeld 25781867	Age 50-59.9 (mean or median) and no subgroup >=60	55.4
McPherson 29905648	Age 50-59.9 (mean or median) and no subgroup >=60	54.6
Morasco 18291290	Age 50-59.9 (mean or median) and no subgroup >=60	59.8
Morasco 21562923	Age 50-59.9 (mean or median) and no subgroup >=60	54.2
Naliboff 21111684	Age 50-59.9 (mean or median) and no subgroup >=60	52.6
Nielsen 28067693	Age 50-59.9 (mean or median) and no subgroup >=60	56
Ompad 2016-44052-004	Age 50-59.9 (mean or median) and no subgroup >=60	55.8
Outlaw 2012-07962-004	Age 50-59.9 (mean or median) and no subgroup >=60	58.5
Painter 29095057	Age 50-59.9 (mean or median) and no subgroup >=60	53.8
Peters 29122425	Age 50-59.9 (mean or median) and no subgroup >=60	57
Radmard 30049329	Age 50-59.9 (mean or median) and no subgroup >=60	58.75
Reid 11929502	Age 50-59.9 (mean or median) and no subgroup >=60	54
Rodgers 22410178	Age 50-59.9 (mean or median) and no subgroup >=60	54
Rojas 29915947	Age 50-59.9 (mean or median) and no subgroup >=60	56
Roland 30589633	Age 50-59.9 (mean or median) and no subgroup >=60	56.1
Rosen 15331811	Age 50-59.9 (mean or median) and no subgroup >=60	NR (but in the 50s)
Rosen 18515693	Age 50-59.9 (mean or median) and no subgroup >=60	53
Rosenthal 30199478	Age 50-59.9 (mean or median) and no subgroup >=60	51
Ruggles 27475945	Age 50-59.9 (mean or median) and no subgroup >=60	50
Scherrer 26755784	Age 50-59.9 (mean or median) and no subgroup >=60	55.4
Sekhon 23746149	Age 50-59.9 (mean or median) and no subgroup >=60	58
Sharan 29244102	Age 50-59.9 (mean or median) and no subgroup >=60	56
Taber 27983881	Age 50-59.9 (mean or median) and no subgroup >=60	55.9
Torres 21451118	Age 50-59.9 (mean or median) and no subgroup >=60	55
Vargas-Schaffer 28340165	Age 50-59.9 (mean or median) and no subgroup >=60	57
Wilder 26566771	Age 50-59.9 (mean or median) and no subgroup >=60	(two clinics reported separately) 55.2, 46.2
Williams 25265035	Age 50-59.9 (mean or median) and no subgroup >=60	59.4
Wilsey 19594846	Age 50-59.9 (mean or median) and no subgroup >=60	57.5
Zywiel 22048093	Age 50-59.9 (mean or median) and no subgroup >=60	56
Vakharia 30547120	Age NR (mean or median) and no subgroup >=60	NR
Vakharia 30918797	Age NR (mean or median) and no subgroup >=60	NR
Williams 29735614	Age NR (mean or median) and no subgroup >=60	NR
West 26660909	Age NR (mean or median) and no subgroup >=60	
Seppala 29402646	Age NR (mean or median) and no subgroup >=60	
Vallerand 106574301	Age NR (mean or median) and no subgroup >=60	
Scherrer 28033519	Age NR (mean or median) and no subgroup >=60	
Adogwa 30292669	Age NR (mean or median) and no subgroup >=60	
Boylan 29681163	Age NR (mean or median) and no subgroup >=60	NR
Bradford 29610897	Age NR (mean or median) and no subgroup >=60	
Chindalore 15943961	Age NR (mean or median) and no subgroup >=60	
Edlund 25180008	Age NR (mean or median) and no subgroup >=60	

Author PMID	Rejection Reason	Mean age
Gaither 27610580	Age NR (mean or median) and no subgroup >=60	
Hadland 30657529	Age NR (mean or median) and no subgroup >=60	
Hamilton 19418342	Age NR (mean or median) and no subgroup >=60	NR
Hernandez 30099175	Age NR (mean or median) and no subgroup >=60	
Hoggatt 2017-14649-001	Age NR (mean or median) and no subgroup >=60	
Huhn 30384321	Age NR (mean or median) and no subgroup >=60	NR
Hyer 19928594	Age NR (mean or median) and no subgroup >=60	
Im 2015-27785-022	Age NR (mean or median) and no subgroup >=60	NR
Lin 30646077	Age NR (mean or median) and no subgroup >=60	NR
Lin 18075408	Age NR (mean or median) and no subgroup >=60	
Lin 26129993	Age NR (mean or median) and no subgroup >=60	NR
Maust 30554562	Age NR (mean or median) and no subgroup >=60	
Maxwell 2011-11276-005	Age NR (mean or median) and no subgroup >=60	NR
Moriya 30395428	Age NR (mean or median) and no subgroup >=60	NR
Mosher 28340259	Age NR (mean or median) and no subgroup >=60	NR
Mowbray 26093503	Age NR (mean or median) and no subgroup >=60	NR
Oliva 22115887	Age NR (mean or median) and no subgroup >=60	NR
Palamar 30553910	Age NR (mean or median) and no subgroup >=60	NR
Parsons 2014-25113-001	Age NR (mean or median) and no subgroup >=60	
Patel 28983558	Age NR (mean or median) and no subgroup >=60	NR
Pierce 29573622	Age NR (mean or median) and no subgroup >=60	NR
Powell 29408153	Age NR (mean or median) and no subgroup >=60	
Sayuk 29327358	Age NR (mean or median) and no subgroup >=60	NR
Shiner 28481727	Age NR (mean or median) and no subgroup >=60	
Vasilenko 28938183	Age NR (mean or median) and no subgroup >=60	
Wall 29220668	Age NR (mean or median) and no subgroup >=60	
Wei 30747958	Age NR (mean or median) and no subgroup >=60	NR
Krebs 2018-12570-001	Comparison of opioid vs non-opioid only (no high-risk subgroups identified or effect modification analyses)	
Basak 31210142	Comparison of opioid vs non-opioid only (no high-risk subgroups identified or effect modification analyses)	
Rose 30471102	Comparison with younger only (not *among* older adults)	NR
Roy 28831278	Comparison with younger only (not *among* older adults)	
Abrams 21609851	Comparison with younger only (not *among* older adults)	NR
Badrakalimuthu 104314645	Comparison with younger only (not *among* older adults)	
Bedard 29292342	Comparison with younger only (not *among* older adults)	NR
Bedard 28917616	Comparison with younger only (not *among* older adults)	NR
Bohnert 21467284	Comparison with younger only (not *among* older adults)	NR
Bohnert 28301070	Comparison with younger only (not *among* older adults)	NR
Boscarino 20712819	Comparison with younger only (not *among* older adults)	NR
Carew 30317161	Comparison with younger only (not *among* older adults)	
Chan 30855717	Comparison with younger only (not *among* older adults)	NR

Author PMID	Rejection Reason	Mean age
Cryar 29705679	Comparison with younger only (not *among* older adults)	
Firoz 15353395	Comparison with younger only (not *among* older adults)	
Gagliese 10969291	Comparison with younger only (not *among* older adults)	
Huang 29161066	Comparison with younger only (not *among* older adults)	NR
Orhurhu 31077526	Comparison with younger only (not *among* older adults)	
Papaleontiou 20533971	Comparison with younger only (not *among* older adults)	
Pillans 28253466	Comparison with younger only (not *among* older adults)	
Rudd 26720857	Comparison with younger only (not *among* older adults)	
Saha 27337416	Comparison with younger only (not *among* older adults)	
Vanderlip 25277462	Comparison with younger only (not *among* older adults)	
Westermeyer 2016-41355-009	Comparison with younger only (not *among* older adults)	
Zautcke 11781905	Comparison with younger only (not *among* older adults)	NR
Al Achkar 29347984	Comparison with younger only (not *among* older adults)	NR
Bartels 2018-23449-011	Comparison with younger only (not *among* older adults)	NR
Bartels 29627407	Comparison with younger only (not *among* older adults)	NR
Bauer 26848633	Comparison with younger only (not *among* older adults)	
Choi 2017-49027-001	Duplicate	
Griffioen 2017-24682-006	Duplicate	
Han 2019-13421-016	Duplicate	
Larney 2015-00317-001	Duplicate	
Neutel 2014-05096-015	Duplicate	
Otten 2011-27935-004	Duplicate	
Park 2011-14318-002	Duplicate	
Shi 2012-15263-006	Duplicate	
Tevik 2018-18441-001	Duplicate	
Zedler 2014-51975-011	Duplicate	
Carew 29136566	Duplicate	
Wu 24163278	Duplicate	
Bedard 28413136	Mean age <65 and no other age info or analyses	NR
Campbell 26011277	Mean age <65 and no other age info or analyses	59
Chang 29523356	Mean age <65 and no other age info or analyses	60.4
Chang 31187888	Mean age <65 and no other age info or analyses	NR
Chenaf 27592608	Mean age <65 and no other age info or analyses	62.7
Hakkinen 25447184	Mean age <65 and no other age info or analyses	NR
Kim 28844770	Mean age <65 and no other age info or analyses	62.4
Knudsen 2011-04767-011	Mean age <65 and no other age info or analyses	62.2
Maree 27567185	Mean age <65 and no other age info or analyses	NR
Pugely 29653244	Mean age <65 and no other age info or analyses	NR
Rose 26431852	Mean age <65 and no other age info or analyses	63
Rosen 21237575	Mean age <65 and no other age info or analyses	NR
Schwarzkopf 26897490	Mean age <65 and no other age info or analyses	61
Sing 27451080	Mean age <65 and no other age info or analyses	61

Author PMID	Rejection Reason	Mean age
Turner 26785321	Mean age <65 and no other age info or analyses	64
Von Korff 28113120	Mean age <65 and no other age info or analyses	64
Wong 22059201	Mean age <65 and no other age info or analyses	52
Tevik 30999872	No opioids	
Tevik 28886172	No opioids	
Tevik 30990815	No opioids	
Almeida 30029154	No opioids	
Arinzon 2006-05685-002	No opioids	
Blazer 105444706	No opioids	
Chhatre 28830504	No opioids	
Choi 25923291	No opioids	
Choi 29560840	No opioids	
Colliver 106460745	No opioids	
Goebel 21256706	No opioids	
Hawkins 22305658	No opioids	
Lau 106601191	No opioids	
Lay 105804666	No opioids	
Reynoso-Vallejo 28853974	No opioids	
Yee 16288080	No opioids	
Zarba 15667402	No opioids	
Zuckerman 16862033	No opioids	
Bosley 14728635	No opioids	75
Gatti 21491171	No outcome of interest	
Glintborg 18344106	No outcome of interest	
Griffioen 27739258	No outcome of interest	
Hollingworth 25845470	No outcome of interest	
Hubbard 25877120	No outcome of interest	
Hwang 27079639	No outcome of interest	
Ilgen 20553655	No outcome of interest	
Jones 27387857	No outcome of interest	
Kann 24842594	No outcome of interest	
Kennedy 21134724	No outcome of interest	
Khalid 29253702	No outcome of interest	
Krantz 15771942	No outcome of interest	
Krebs 28893675	No outcome of interest	
Lewis 20624241	No outcome of interest	
Loughrey 12850423	No outcome of interest	
Malte 29287034	No outcome of interest	
McAlpine 18374970	No outcome of interest	
Minner 106496731	No outcome of interest	
Morasco 26516794	No outcome of interest	
Muench 31008896	No outcome of interest	

Author PMID	Rejection Reason	Mean age
Namba 29934272	No outcome of interest	
Nelson 22266156	No outcome of interest	
Pasquale 24268019	No outcome of interest	
Pergolizzi 2011-14318-003	No outcome of interest	
Tiet 2015 26075352	No outcome of interest	
Zhao 30653178	Not high-income country	
Safaei 19260339	Not high-income country	
Ping 27023332	Not high-income country	
Sharma 11868024	Not high-income country	
Mattson 28650597	Not primary study or SR	
Atkinson 24161287	Not primary study or SR	
Bush 26913328	Not primary study or SR	
Green 2017-39484-002	Not primary study or SR	
Licht 19947072	Not primary study or SR	
O'Neil 23036838	Not primary study or SR	
Pollice 18547496	Not primary study or SR	
Salmon 104515908	Not primary study or SR	
Taylor 23251860	Not primary study or SR	
105902518	Not primary study or SR	
Joshi 30718033	Not primary study or SR	
Cherrier 2009-15780-001	Opioid effectiveness study of pain control only (not misuse or decreasing opioid use)	
da Costa 25229835	Opioid effectiveness study of pain control only (not misuse or decreasing opioid use)	
Dauri 24567278	Opioid effectiveness study of pain control only (not misuse or decreasing opioid use)	
Grieff 26943250	Opioid effectiveness study of pain control only (not misuse or decreasing opioid use)	
Kaczocha 29486720	Opioid effectiveness study of pain control only (not misuse or decreasing opioid use)	
Karlsson 19393841	Opioid effectiveness study of pain control only (not misuse or decreasing opioid use)	
Leegaard 21099695	Opioid effectiveness study of pain control only (not misuse or decreasing opioid use)	
Otten 22124189	Opioid effectiveness study of pain control only (not misuse or decreasing opioid use)	
Roth 10737286	Opioid effectiveness study of pain control only (not misuse or decreasing opioid use)	
Vorsanger 2011-18891-005	Opioid effectiveness study of pain control only (not misuse or decreasing opioid use)	

Abbreviaton: PMID = PubMed identifier.

Table E-2. Articles that did not report multivariable analyses or on interventions

Author	PMID (or Other Identifier)
Abraham	30665272
Abrahamsen	18690484
Axeen	29532477
Azim	25599456
Bachhuber	26728642
Barbera	22370317
Baser	23809020
Becker	19425211
Becker	28410338
Berecki-Gisolf	27624336
Birke	26861026
Blazer	19486199
Brennan	23659899
Brennan	27384953
Brooks	31134673
Campbell	30676931
Cepeda	22339505
Chang	104903112
Cheah	28735841
Chenaf	27363310
Clarke	24519537
Cotton	28562400
Culberson	104903118
Dalleur	23044639
Deyo	29521813
Du	27855095
Dufour	24289539
Edgell	2000-08050-005
Edlund	20634006
Gadzhanova	24002742
Gellad	27925868
Giannitrapani	29059412
Grossbard	24969956
Guo	20625617
Han	2019-22070-020
Han	23956137
Han	26584180
Han	30197051
Han	30763631
Hawkins	2015-47083-011
Hawkins	26332513

Author	PMID (or Other Identifier)
Hayes	30039181
Hereford	29909957
Hernandez	28392133
Hernandez	29402712
Hirji	30625257
Ho	29452704
Hsia	29975257
Huang	29174762
Ilgen	2016-49078-013
Jeffery	30068513
Jin	31251985
LeResche	26153668
Miller	25686208
Mont	28802777
Mosher	25519224
Namba	28974377
Neutel	23900890
Neutel	24201229
Nguyen	30667135
Pesa	24991356
Petrò	2016-12267-001
Politzer	29198871
Pugh	16981799
Puustinen	22044595
Redding	25455930
Reid	20642732
Rockett	16669904
Roxburgh	21895598
Roxburgh	23442164
Rudisill	27027152
Sabatino	29406338
Salib	24931787
Schepis	2016-26226-038
Schepis	29624517
Schepis	29940388
Schuurmans	12764718
Serdarevic	30145703
Simoni-Wastila	16492661
Simpson	31036710
Smith	27631068
Spitz	21752299

Author	PMID (or Other Identifier)
Steinman	2015-07011-016
Sundseth	29656692
Svider	29446449
Tang	27162807
Trist	28096225
Upadhyay	18539764
Vu	29797421
Wan	26005516
West	25678441
Wilke	30928332
Wolf	28279159
Woo	20114135
Wyse	30878769
Zarling	27161903
Zedler	24931395
Zedler	26077738
Zhang	30206790
Zhao	21951753
Zheng	30790376

Abbreviation: PMID = PubMed identifier.